BMJ Open

The relationship between ambulatory blood pressure variability and enlarged perivascular spaces: a cross-sectional study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2016-015719
Article Type:	Research
Date Submitted by the Author:	26-Dec-2016
Complete List of Authors:	Yang, Shuna; Beijing Chaoyang Hospital, Neurology Qin, Wei; Beijing Chaoyang Hospital, Neurology Yang, Lei; Beijing Chaoyang Hospital, Neurology Fan, Huimin; Beijing Chaoyang Hospital, Neurology Li, Yue; Beijing Chaoyang Hospital, Neurology Yin, Jiangmei; Beijing Chaoyang Hospital, Neurology Hu, Wenli; Neurology
Primary Subject Heading:	Neurology
Secondary Subject Heading:	Health services research
Keywords:	cerebral small vessel disease, enlarged perivascular spaces, Virchow-Robin spaces, blood pressure variability, ambulatory blood pressure monitoring

The relationship between ambulatory blood pressure variability and enlarged perivascular spaces: a cross-sectional study

Shuna Yang[1], Wei Qin[1], Lei Yang[1], Huimin Fan[1], Yue Li[1], Jiangmei Yin[1], Wenli Hu[1*]

1: Department of Neurology, Beijing Chaoyang Hospital, Capital Medical University, Beijing, China

*: Corresponding Author

Email: huwenli@sina.com, Telephone: +8601085231376, Fax: 011-86-10-65926388

Institution address: Beijing Chaoyang Hospital, No.8 South Gongti Road, Chaoyang District, Beijing, China

Abstract

Objectives: Recent studies reported that 24-hour ambulatory blood pressure variability (ABPV) was associated with lacunar brain infarction and white matter hyperintensities (WMH). However, the relationship between ABPV and enlarged perivascular spaces (EPVS) hasn't been investigated. So in the study, we aimed to investigate whether ABPV was associated with EPVS by 24-hour ambulatory blood pressure monitoring (24h ABPM).

Design: We conducted this study as a cross-sectional study.

Settings: The study was based on patients for physical examinations in our hospital from May 2013 to Jun 2016.

Participants: Patients with both brain MRI scans and 24h ABPM were included and patients with acute stroke, a history of severe stroke and some other severe diseases were excluded. A total of 573 Chinese were prospectively enrolled in this study.

Primary and secondary outcome measures: EPVS in basal ganglia (BG) and white matter (WM) were identified on MRI and classified into three categories by the severity. WMH were scored by Fazekas scale. Spearman correlation analysis and multivariate logistic regression analyses were used to determine the relationship between ABP levels and EPVS.

Results: There were statistical differences in all of the following ABPV metrics: 24h, daytime, nighttime systolic blood pressure standard deviation (SBP-SD), systolic blood pressure coefficient of variation (SBP-CV) and diastolic blood pressure coefficient of variation (DBP-CV) and nighttime DBP-SD among the three subgroups stratified by EPVS severity in BG ($p < 0.05$). The above ABPV metrics were linearly associated with the degree of EPVS in BG by spearman correlation analysis. The association between ABPV and EPVS in BG was unchanged after controlling for confounders. The results of spearman correlation analysis showed ABPV weren't related to the degree of EPVS in WM.

Conclusion: ABPV was linearly associated with EPVS in BG, but not in WM. Pathogenesis of EPVS in BG and WM may be different.

Keywords cerebral small vessel disease, enlarged perivascular spaces, Virchow-Robin spaces, blood pressure variability, ambulatory blood pressure monitoring

Strengths and limitations of this study

- Assessments of EPVS and WMH were performed by two experienced neurologists blinded to clinical information and disagreements were resolved by consensus, which ensure the accuracy of the assessments.
- Detailed information on some confounders crucial to the interpretation of EPVS was collected and multivariate logistic regression analyses were performed to determine the independency of association.
- The study was based on hospital physical examinations people in a single center and the cohort may not represent the general population.
- This was a cross-sectional study, and the causal relationship between ABPV and EPVS could not be established.

INTRODUCTION

Perivascular spaces, or Virchow-Robin spaces, are perivascular compartments surrounding the small penetrating cerebral vessels, serving as an important drainage system for interstitial fluid and solute in brain[1]. They can dilate with accumulation of the interstitial fluid[2, 3]. Enlarged perivascular spaces (EPVS) appear as punctate or linear signal intensities similar to cerebrospinal fluid (CSF) on all MRI sequences in white matter (WM), basal ganglia (BG), hippocampus and brainstem[4, 5]. Recent studies indicated that EPVS were a magnetic resonance imaging (MRI) marker of cerebral small vessel diseases (CSVD) and were associated with other morphological features of CSVD such as white matter hyperintensities (WMH) and lacunes[6, 7]. Some studies found EPVS were associated with impaired cognitive function[5], incident

dementia[8] and sleep disorders[9]. Therefore, it is of clinical importance to understand the risk factors of EPVS and search for treatable methods.

24-hour ambulatory blood pressure monitoring (24-h ABPM) is proven to be a more useful and scientific method to predict blood pressure-related brain damage than single office blood pressure measurements[10, 11]. Ambulatory blood pressure variability (ABPV) could be well documented by 24-h ABPM. Previous studies demonstrated higher ABPV increased the risk of cardiovascular events[12, 13], WMH, lacunar infarction, and cognitive decline[14, 15]. WMH, lacunar infarction and EPVS are all neuroimaging features of CSVD and share some risk factors, such as age and hypertension[16]. However, the relationship between ABPV and EPVS has never been investigated. So in the study, we aimed to investigate whether ABPV was associated with EPVS by 24-h ABPM.

METHODS

Study subjects

We conducted this study as a cross-sectional study. The patients meeting both inclusion and exclusion criteria for physical examinations were prospectively enrolled to avoid selection bias in Beijing Chaoyang Hospital Affiliated to Capital Medical University from May 2013 to Jun 2016. The number of arriving patients during the study period, inclusion and exclusion criteria determined the sample size. Inclusion criteria were: (1) patients undergo brain MRI scans; (2) patients undergo 24-h ABPM; (3) the interval of brain MRI scans and 24-h ABPM was less than 1 month; (4) patients agreed to participate in our study and sign an informed consent. The following patients were excluded: (1) patients with acute stroke, Parkinson disease, dementia, severe traumatic or toxic or infectious brain injury, and brain tumor; (2) patients with severe heart disease, recent myocardial infarction or angina pectoris disorders, severe infections, severe nephrosis or liver disease, thrombotic diseases and tumor; (3) patients with history of severe ischemic (the largest diameter of infarct size ＞20mm on diffusion-weighted imaging and fluid attenuated inversion recovery) or hemorrhagic stroke because of difficulty assessments on EPVS; (4) patients with

invalid 24-h ABPM data (The 24-h ABPM data were considered invalid if measurement was < 70%, < 1 measurement per hour during daytime, and < 6 in total during nighttime).

Assessments of EPVS and WMH

The neurological image examinations were performed in Radiology Department of Beijing Chaoyang Hospital Affiliated to Capital Medical University. MR imagings were acquired on 3.0 T Siemens scanner (Erlangen, Germany). Assessments of EPVS and white matter hyperintensitis (WMH) were performed by two experienced neurologists blinded to clinical information to avoid bias. Disagreements were resolved by consensus.

EPVS were defined as CSF-like signal intensity lesions of round, ovoid, or linear shape of <3mm and located in areas supplied by perforating arteries[6, 17]. We distinguished lacune from EPVS by their larger size (>3mm), spheroid shape and surrounding hyperintensities on FLAIR. WMH were defined as hyperintense signals on T2-weighted and FLAIR and decreased signal intensities on T1-weighted MR imaging.

EPVS in BG and WM were separately assessed according to the scales which were used in other studies[18, 19]. In BG, EPVS were rated according to the number in the slice containing the maximum amount of EPVS. The grades of EPVS were rated as follows: grade 1: < 5 EPVS, grade 2: 5 to 10 EPVS, grade 3: > 10 but still countable, and grade 4: infinite number of EPVS. In WM, EPVS were scored as follows: grade 1：<10 EPVS in total WM, grade 2：>10 in total WM and <10 in the slice containing the maximum number of EPVS, grade 3：10 to 20 EPVS in the slice containing the

maximum number of EPVS, grade 4：> 20 in the slice containing the maximum number of EPVS. We classified EPVS into three categories: degree 1 = grade 1; degree 2 = grade 2; degree 3 = grade 3 or 4.

WMH were scored by Fazekas scale. The detailed description of assessment has been previously published[20]. Periventricular and deep WMH were evaluated separately and totaled together as Fazekas scores.

24-hour ambulatory blood pressure monitoring

24-h ABPM was performed using an automated system (FB-250; Fukuda Denshi, Tokyo, Japan). BP was measured every 30 minutes during the daytime (8:00 AM to 11:00 PM) and every 60 minutes during the nighttime (11:00 PM to 8:00 AM). We excluded a 2-hour transition period around the reported rising and retiring times. Mean 24-h, daytime, and nighttime systolic and diastolic blood pressure coefficient of variation (CV) and standard deviation (SD) were collected. The CV value was defined as the ratio between the SD and the mean systolic blood pressure (SBP) or diastolic blood pressure (DBP) at the same periods. SD and CV were considered as metrics of BPV in this study. Patients continued their previous medication, and we registered the use of anti-hypertension drugs.

Statistical analysis

Continuous variables were presented as mean values ± SD and compared with ANOVA for factors with a normal distribution, whereas no normally distributed variables were compared with Kruskal–Wallis test as appropriate. Categorical variables were expressed as percentages and compared using the chi-square test.

Spearman correlation analysis was used to calculate the association between ABPV and the severity of EPVS. In addition, multivariate logistic regression analyses were performed to determine whether the ABPV were independently associated with EPVS after adjustment for other confounders. The results were based on valid data; missing data were excluded. Analyses were performed with Statistical Package for Social Sciences (SPSS version21.0), and statistical significance was accepted at the $p < 0.05$.

RESULTS

Baseline characteristics of the study participants

742 patients undergo both brain MRI scans and 24-h ABPM within 1 month in Beijing Chaoyang Hospital Affiliated to Capital Medical University from May 2013 to Jun 2016. 40 patients were excluded because of acute stroke, 21 were excluded because of history of severe or hemorrhagic stroke, 15 were excluded because of a history of tumor and 93 were excluded because of invalid ABPM data, leaving 573 patients for the present study. None of them had missing data. Table 1 showed the characteristics of all subjects and different subgroups stratified by EPVS severity in BG and WM. Age, Fazekas scale, proportion of hypertension and stroke/TIA, levels of blood urea nitrogen and creatinine increased with the degree of EPVS in BG increasing. There were statistical differences in age, Fazekas scale and proportion of coronary artery atherosclerosis disease (CAD) among subgroups based on EPVS degree in WM.

Table 1. General characteristics of all subjects and subgroups stratified by EPVS severity

Characteristics	All patietns	EPVS in BG			EPVS in WM		
		Degree 1	Degree 2	Degree 3	Degree 1	Degree 2	Degree 3
n	573	244	179	150	200	207	166
Age, years	67.8±14.8	61.4±14.4**	67.6±13.8**	78.3±9.6**	70.45±15.2**	66.25±14.4**	66.46±14.3**
Sex, male (%)	355 (62.0)	143 (58.6)	108 (60.3)	104 (69.3)	115 (57.5)	128 (61.8)	112 (67.5)
Current smoking (%)	162 (28.3)	83 (34.0)*	61(34.1)*	18(12.0)*	52 (26.0)	60 (29.0)	50 (30.1)
Current alcohol (%)	126 (22.0)	62 (25.4)*	45 (25.1)*	19 (12.7)*	36 (18.0)	50 (24.2)	40 (24.1)
Hypertension (%)	420 (73.3)	170 (69.7)*	122 (68.2)*	128 (85.3)*	150 (75.0)	145 (70.5)	125 (74.7)
Diabetes (%)	191 (33.3)	78 (32.0)	59 (33.0)	54 (36.0)	71 (35.5)	62 (30.0)	58 (34.9)
CAD (%)	140 (24.4)	48 (19.7)	48 (26.8)	44 (29.3)	61 (30.5) *	45 (21.7) *	34 (20.5) *
Stroke or TIA (%)	125 (21.8)	40 (16.4)**	33 (18.4)**	52 (34.7)**	49 (24.5)	39 (18.8)	37 (22.2)
BMI, kg/m^2	25.6±3.5	25.6±3.4	25.3±3.5	25.8±3.5	25.8±3.4	25.4±3.5	25.5±3.5
HDL, mmol/L	1.2±0.4	1.2±0.4	1.2±0.4	1.2±0.3	1.2±0.4	1.2±0.4	1.2±0.3
LDL, mmol/L	2.5±0.8	2.5±0.8	2.5±0.8	2.3±08	2.4±0.8	2.4±0.8	2.5±0.7
HbA1, %	6.4±1.3	6.4±1.3	6.4±1.4	6.5±1.2	6.4±1.1	6.5±1.4	6.5±1.4
BUN, mmol/L	5.8±2.1	5.5±1.7**	5.9±2.6**	6.3±2.0**	6.0±2.5	5.7±1.9	5.8±1.9
Creatinine, umol/L	79.1±27.1	74.0±19.3**	81.7±32.6**	84.2±29.4**	81.2±27.4	77.7±27.3	78.3±26.4
Fazekas scale	3.1±1.8	2.2±1.4**	3.1±1.7**	4.7±1.5**	3.5±2.0**	2.9±1.7**	3.1±1.7**
Using of anti-hypertensive drugs (%)	342 (59.7)	130 (53.3) *	96 (53.6) *	116 (77.3) *	129 (64.5)	114 (55.1)	99 (59.6)

EPVS, enlarged perivascular spaces; BG, basal ganglia; WM, white matter; BMI, body mass index; CAD, coronary artery atherosclerosis disease; TIA, transient ischemic attack; HDL, high-density lipoprotein; LDL, low-density lipoprotein; HbA1c, hemoglobin A1c; BUN, blood urea nitrogen. * $p < 0.05$, * * $p < 0.01$.

Association between ABPV and EPVS in BG

Ambulatory blood pressure SD and CV of EPVS in BG were presented in Table 2. There were statistical differences ($p < 0.05$) in all of the following BPV metrics: 24h,

daytime, nighttime SBP-SD, SBP-CV, DBP-CV and nighttime DBP-SD among the three subgroups stratified by EPVS severity in BG. In addition, theses metrics gradually increased with the degree of EPVS increasing (Fig 1-3). The results of spearman correlation analysis demonstrated theses metrics were linearly associated with the degree of EPVS in BG (Table 3). The association between ABPV and EPVS were unchanged after controlling for demographic confounders (model 1) and Fazekas scale (model 2). The results of multiple logistic regression analysis were presented in Table 4.

Association between ABP Levels and EPVS in WM

Ambulatory blood pressure SD and CV of EPVS in WM were also presented in Table 2. There were statistical differences ($p < 0.05$) in 24h and daytime SBP-SD, DBP-SD, SBP-CV and DBP-CV among the three subgroups stratified by EPVS severity in WM. However, there were not linear trend among the three subgroup stratified by EPVS severity. The results of spearman correlation analysis showed there were no linear correlation between theses metrics and the degree of EPVS in WM (Table 3).

Table 2. Results of ABPV in all subjects and subgroups stratified by EPVS severity

	All patietns	EPVS in BG			EPVS in WM		
		Degree 1	Degree 2	Degree 3	Degree 1	Degree 2	Degree 3
24h							
SBP-SD, mmHg	18.28±5.27	16.93±4.76**	18.57±4.56**	20.13±6.21**	18.86±5.56**	17.36±5.11**	18.73±4.99**
DBP-SD, mmHg	12.56±3.58	12.22±3.56	12.62±3.34	13.05±3.86	12.83±3.76**	11.85±3.32**	13.14±3.56**
SBP-CV, %	13.83±3.80	13.21±3.56**	13.99±3.54**	14.64±4.26**	14.16±3.87*	13.23±3.70*	14.18±3.76*

DBP-CV, %	16.68±4.74	16.03±4.68*	16.82±4.46*	17.55±5.04*	17.22±4.76**	15.78±4.72**	17.14±4.60**
Daytime							
SBP-SD, mmHg	18.02±5.70	16.66±4.93**	18.21±5.35**	19.99±6.65**	18.68±5.98**	16.99±5.47**	18.50±5.49**
DBP-SD, mmHg	12.56±4.01	12.25±3.80	12.51±3.93	13.12±4.40	12.81±4.06**	11.76±3.71**	13.26±4.17**
SBP-CV, %	13.45±4.08	12.84±3.75**	13.62±4.14**	14.26±4.38**	13.86±4.16*	12.76±3.88*	13.81±4.12*
DBP-CV, %	16.48±5.19	15.84±4.77*	16.47±5.24*	17.54±5.63*	16.98±4.88**	15.47±5.12**	17.15±5.48**
Nighttime							
SBP-SD, mmHg	15.21±7.37	13.79±7.71**	15.18±5.74**	17.54±7.97**	15.08±6.09	14.94±8.66	15.69±7.05
DBP-SD, mmHg	10.43±4.50	9.81±4.33*	10.77±4.55*	11.03±4.61*	10.23±4.11	10.26±4.58	10.88±4.84
SBP-CV, %	11.85±5.37	11.22±5.53**	11.77±4.56**	12.95±5.84**	11.69±4.62	11.70±5.95	12.23±5.48
DBP-CV, %	14.26±6.02	13.42±5.88**	14.75±5.89**	15.03±628**	14.20±5.61	14.08±6.30	14.54±6.17

SBP: systolic blood pressure; DBP: diastolic blood pressure; CV: coefficient of variation; SD: standard deviation. * $P < 0.05$, * * $P < 0.01$.

Table 3. Results of spearman correlation analyses between the degree of EPVS and ABPV

	EPVS in BG		EPVS in WM	
	r	P value	r	P value
24h				
SBP-SD	0.216	0.000	-0.013	0.762
DBP-SD	0.082	0.051	0.030	0.481
SBP-CV	0.137	0.001	-0.008	0.854
DBP-CV	0.123	0.003	-0.028	0.505
Daytime				
SBP-SD	0.205	0.000	-0.024	0.562

DBP-SD	0.065	0.120	0.031	0.459
SBP-CV	0.135	0.001	-0.023	0.585
DBP-CV	0.109	0.009	-0.017	0.679
Nighttime				
SBP-SD	0.229	0.000	0.020	0.637
DBP-SD	0.125	0.003	0.043	0.309
SBP-CV	0.136	0.001	0.027	0.521
DBP-CV	0.135	0.001	0.007	0.870

SBP: systolic blood pressure; DBP: diastolic blood pressure; CV: coefficient of variation; SD: standard deviation.

Table 4. Results of multivariate logistic regression analyses between ABPV and EPVS in BG (Degree 3 vs. Degree 1)

	Model 1		Model 2	
	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value
24h				
SBP-SD	1.135(1.081, 1.191)	0.000	1.129(1.070, 1.191)	0.000
SBP-CV	1.121(1.052, 1.194)	0.000	1.138(1.060, 1.222)	0.000
DBP-CV	1.075(1.022, 1.130)	0.005	1.091(1.031, 1.154)	0.002
Daytime				
SBP-SD	1.110(1.063, 1.160)	0.000	1.109(1.057, 1.164)	0.000
SBP-CV	1.083(1.022, 1.147)	0.007	1.096(1.028, 1.169)	0.005
DBP-CV	1.069(1.021, 1.119)	0.005	1.088(1.035, 1.145)	0.001
Nighttime				
SBP-SD	1.071(1.034, 1.108)	0.000	1.062(1.025, 1.101)	0.001
DBP-SD	1.102(1.044, 1.163)	0.000	1.096(1.034, 1.161)	0.002
SBP-CV	1.073(1.027, 1.121)	0.002	1.076(1.027, 1.127)	0.002
DBP-CV	1.052(1.012, 1.094)	0.011	1.060(1.015, 1.106)	0.008

Results of multiple regression analyses presented as OR per 1% increase in BP-CV and 1mmHg in BP-SD

Reference group: degree 1 subgroup of EPVS in BG.

Model1: adjusted for age, smoking, alcohol, hypertension, stroke/TIA, BUN and creatinine and using of anti-hypertensive drugs.

Model2: model 1 + Fazekas scale.

DISCUSSION

In this study, we explored the relationship between ABPV and EPVS based on hospital physical examinations population. Our data suggested that all of the following metrics: 24h, daytime and nighttime SBP-SD, SBP-CV and DBP-CV were linearly associated with the degree of EPVS in BG. The association between the above ABPV metrics and EPVS in BG were unchanged after controlling for demographic confounders and Fazekas scale. Although there were statistical differences in 24h and daytime ABPV metrics among the three subgroups stratified by EPVS severity in WM, there were not linear correlation between ABPV and the degree of EPVS in WM. In addition, we found age, Fazekas scale, hypertension, stroke/transient ischemic attack (TIA), levels of blood urea nitrogen and creatinine were positively associated with the degree of EPVS in BG.

There were methodological strengths of our study. We recruited participants strictly according to inclusion and exclusion criteria to avoid selection bias. In addition, assessments of EPVS and WMH were performed by two experienced neurologists blinded to clinical information and disagreements were resolved by consensus, which

ensure the accuracy of the assessments. We collected detailed information on vascular confounders, WMH, levels of blood urea nitrogen and creatinine, which are crucial to the interpretation of EPVS[6, 21]. So we think the reliability of the data is high. There were some limitations in our study. First, our study was based on hospital physical examinations people in a single center and the cohort may not represent the general population. Second, this was a cross-sectional study, and the causal relationship between ABPV and EPVS could not be established. Third, all participants undergo 24h ABPM which could only show short-term ABPV. It has been demonstrated that the prognostic significance of BPV on vascular diseases is weaker for short-term than for long-term BPV[22].

This is the first study to investigate the relationship between ABPV and EPVS. Previously, several studies investigated the relationship between EPVS and hypertension. In a prospective, multicenter, hospital-based study, Zhang CQ et al[19] found hypertension was associated with the severity of EPVS in WM, not in BG. Pim K et al[23] investigated the association between ABP levels and EPVS in first-ever lacunar stroke patients. Their study found higher day systolic, day diastolic and 24-h diastolic ABP levels were independently associated EPVS in BG, and no relation between ABP levels and EPVS in WM. Our data suggested that 24h, daytime and nighttime SBP-SD, SBP-CV and DBP-CV were linearly associated with the degree of EPVS in BG, but not in WM. The present study couldn't explain the phenomenon. This may be caused by different pathogenesis of EPVS at the different locations. Previous studies have demonstrated higher ABPV increased the risk of neuroimaging

features of CSVD, such as WMH and lacunar infarction[14, 15]. Our results found higher ABPV was independently with higher degree of EPVS in BG, which support the notion that EPVS in BG are a separate marker of CSVD.

An increased permeability of the small vessel walls and blood brain barrier (BBB) are considered to contribute to the development of EPVS, which has been reported to be associated with damage of microvascular endothelial cells and their tight junctions[1, 16, 24]. Higher ABPV would lead to more mechanical stress on the wall vessel, endothelial injury[25] and arterial stiffness[26]. So, it is reasonable that high ABPV contribute to the development of EPVS by the damage to endothelial cell. Our results may remind clinicians that reducing patients' ABPV is as important as reducing patients' high blood pressure levels. In the future, the causal relationship between ABPV and EPVS should be established in a cohort study. And the relationship between ABPV and EPVS should be explored.

CONCLUSION

24h, daytime and nighttime SBP-SD, SBP-CV and DBP-CV were linearly associated with the degree of EPVS in BG. The association was unchanged after controlling for confounders. No relation was found between ABPV and EPVS in WM. It is important for clinicians to reduce both patients' high blood pressure levels and ABPV.

Contributors WH conceived and designed the experiments. SY, WQ, LY and HF participated in the data collection. JY and YL participated in the analysis of the data. SY drafted the manuscript. WH has given final approval of the version to be published. All authors read and approved the final manuscript.

Funding This work is supported by National Natural Science Foundation of China (Grant No. 81271309).

Conflict of Interest None declared.

Ethic approval The study was approved by the Ethics Committee of Beijing Chaoyang Hospital Affiliated to Capital Medical University and was performed in accordance with the declaration of Helsinki.

Acknowledgements

The authors thank all the study participants.

Data sharing statement No additional data are available.

Reference

1. Kwee RM, Kwee TC. Virchow-robin spaces at mr imaging. *Radiographics : a review publication of the Radiological Society of North America, Inc*. 2007;27:1071-1086
2. Ozturk MH, Aydingoz U. Comparison of mr signal intensities of cerebral perivascular (virchow-robin) and subarachnoid spaces. *Journal of computer assisted tomography*. 2002;26:902-904
3. Abbott NJ. Evidence for bulk flow of brain interstitial fluid: Significance for physiology and pathology. *Neurochemistry international*. 2004;45:545-552
4. Zhu YC, Dufouil C, Mazoyer B, et al. Frequency and location of dilated virchow-robin spaces in elderly people: A population-based 3d mr imaging study. *AJNR. American journal of neuroradiology*. 2011;32:709-713
5. Maclullich AM, Wardlaw JM, Ferguson KJ, et al. Enlarged perivascular spaces are associated with cognitive function in healthy elderly men. *Journal of neurology, neurosurgery, and psychiatry*. 2004;75:1519-1523
6. Wardlaw JM, Smith EE, Biessels GJ, et al. Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. *The Lancet. Neurology*. 2013;12:822-838
7. Doubal FN, MacLullich AM, Ferguson KJ, et al. Enlarged perivascular spaces on mri are a feature of cerebral small vessel disease. *Stroke*. 2010;41:450-454
8. Zhu YC, Dufouil C, Soumare A, et al. High degree of dilated virchow-robin spaces on mri is associated with increased risk of dementia. *Journal of Alzheimer's disease : JAD*. 2010;22:663-672
9. Berezuk C, Ramirez J, Gao F, et al. Virchow-robin spaces: Correlations with

polysomnography-derived sleep parameters. *Sleep*. 2015;38:853-858

10. Ohkubo T, Hozawa A, Nagai K, et al. Prediction of stroke by ambulatory blood pressure monitoring versus screening blood pressure measurements in a general population: The ohasama study. *Journal of hypertension*. 2000;18:847-854
11. Shimada K, Kawamoto A, Matsubayashi K, et al. Silent cerebrovascular disease in the elderly. Correlation with ambulatory pressure. *Hypertension (Dallas, Tex. : 1979)*. 1990;16:692-699
12. Conen D, Bamberg F. Noninvasive 24-h ambulatory blood pressure and cardiovascular disease: A systematic review and meta-analysis. *Journal of hypertension*. 2008;26:1290-1299
13. Rothwell PM. Does blood pressure variability modulate cardiovascular risk? *Current hypertension reports*. 2011;13:177-186
14. Yamaguchi Y, Wada M, Sato H, et al. Impact of ambulatory blood pressure variability on cerebral small vessel disease progression and cognitive decline in community-based elderly japanese. *American journal of hypertension*. 2014;27:1257-1267
15. Filomena J, Riba-Llena I, Vinyoles E, et al. Short-term blood pressure variability relates to the presence of subclinical brain small vessel disease in primary hypertension. *Hypertension (Dallas, Tex. : 1979)*. 2015;66:634-640; discussion 445
16. Wardlaw JM, Smith C, Dichgans M. Mechanisms of sporadic cerebral small vessel disease: Insights from neuroimaging. *The Lancet. Neurology*. 2013;12:483-497
17. Groeschel S, Chong WK, Surtees R, et al. Virchow-robin spaces on magnetic resonance images: Normative data, their dilatation, and a review of the literature. *Neuroradiology*. 2006;48:745-754
18. Zhu YC, Tzourio C, Soumare A, et al. Severity of dilated virchow-robin spaces is associated with age, blood pressure, and mri markers of small vessel disease: A population-based study. *Stroke*. 2010;41:2483-2490
19. Zhang C, Chen Q, Wang Y, et al. Risk factors of dilated virchow-robin spaces are different in various brain regions. *PloS one*. 2014;9:e105505
20. Fazekas F, Chawluk JB, Alavi A, et al. Mr signal abnormalities at 1.5 t in alzheimer's dementia and normal aging. *AJR. American journal of roentgenology*. 1987;149:351-356
21. Yamamoto Y, Ohara T, Nagakane Y, et al. Chronic kidney disease, 24-h blood pressure and small vessel diseases are independently associated with cognitive impairment in lacunar infarct patients. *Hypertension research : official journal of the Japanese Society of Hypertension*. 2011;34:1276-1282
22. Rothwell PM, Howard SC, Dolan E, et al. Prognostic significance of visit-to-visit variability, maximum systolic blood pressure, and episodic hypertension. *Lancet (London, England)*. 2010;375:895-905
23. Klarenbeek P, van Oostenbrugge RJ, Lodder J, et al. Higher ambulatory blood pressure relates to enlarged virchow-robin spaces in first-ever lacunar stroke patients. *Journal of neurology*. 2013;260:115-121
24. Wuerfel J, Haertle M, Waiczies H, et al. Perivascular spaces--mri marker of inflammatory activity in the brain? *Brain : a journal of neurology*. 2008;131:2332-2340
25. Diaz KM, Veerabhadrappa P, Kashem MA, et al. Visit-to-visit and 24-h blood pressure variability: Association with endothelial and smooth muscle function in african americans. *Journal of human hypertension*. 2013;27:671-677
26. Schillaci G, Bilo G, Pucci G, et al. Relationship between short-term blood pressure variability

and large-artery stiffness in human hypertension: Findings from 2 large databases. *Hypertension (Dallas, Tex. : 1979)*. 2012;60:369-377

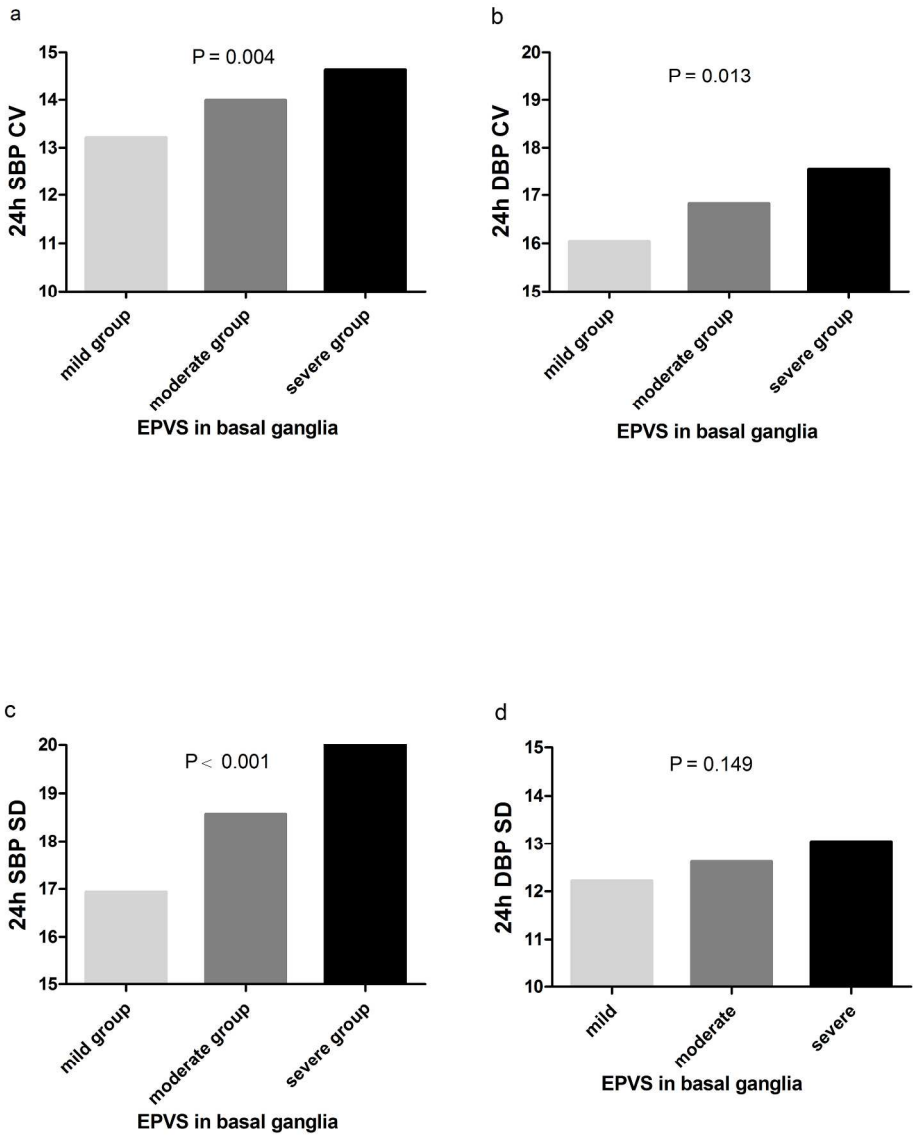


Figure 1. 24h mean ABPV metrics of subgroups stratified by EPVS severity in BG. (a) CV of 24h mean systolic blood pressure. (b) CV of 24h mean diastolic blood pressure. (c) SD of 24h mean systolic blood pressure. (d) SD of 24h mean diastolic blood pressure.

237x292mm (300 x 300 DPI)

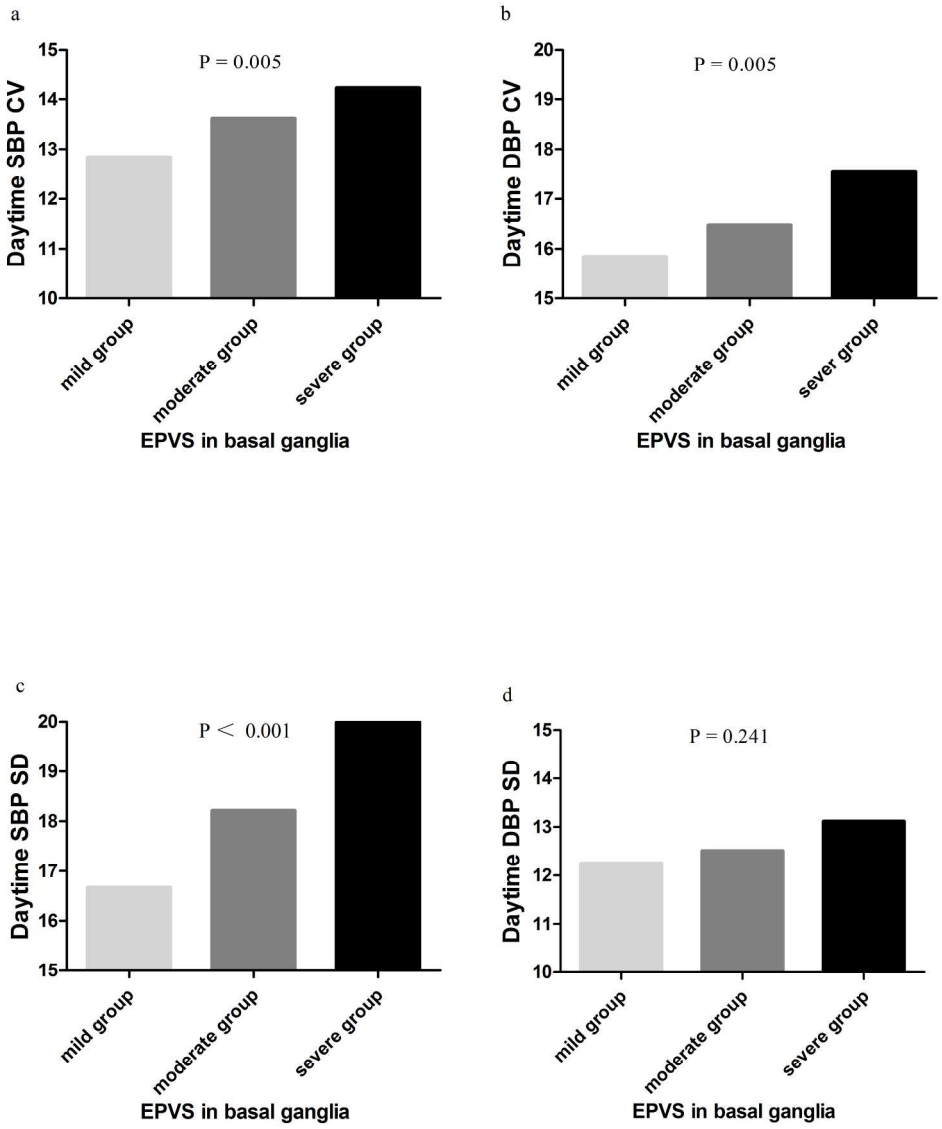


Figure 2. Daytime mean ABPV metrics of subgroups stratified by EPVS severity in BG. (a) CV of daytime mean systolic blood pressure. (b) CV of daytime mean diastolic blood pressure. (c) SD of daytime mean systolic blood pressure. (d) SD of daytime mean diastolic blood pressure.

227x271mm (300 x 300 DPI)

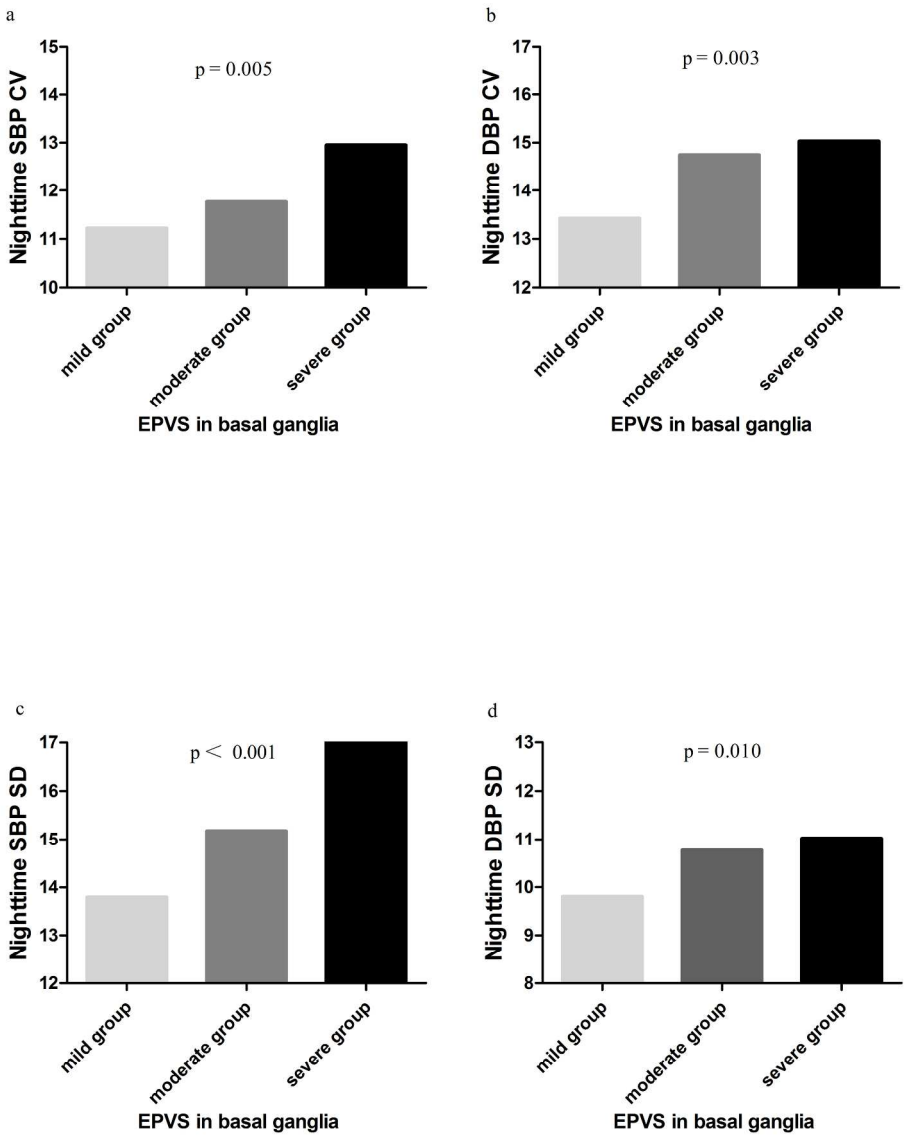


Figure 3. Nighttime mean ABPV metrics of subgroups stratified by EPVS severity in BG. (a) CV of nighttime mean systolic blood pressure. (b) CV of nighttime mean diastolic blood pressure. (c) SD of nighttime mean systolic blood pressure. (d) SD of nighttime mean diastolic blood pressure.

236x294mm (300 x 300 DPI)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	P1 and 2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	P2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	P3-4
Objectives	3	State specific objectives, including any prespecified hypotheses	P4
Methods			
Study design	4	Present key elements of study design early in the paper	P4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	P4
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	P4
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	P5-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	P5-6
Bias	9	Describe any efforts to address potential sources of bias	P4 and 5

Study size	10	Explain how the study size was arrived at	P4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	P6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	P6-7
		(*b*) Describe any methods used to examine subgroups and interactions	P6-7
		(*c*) Explain how missing data were addressed	P7
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	P7
		(b) Give reasons for non-participation at each stage	P7
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	P7-8
		(b) Indicate number of participants with missing data for each variable of interest	P7
Outcome data	15*	Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	P9-12
		(*b*) Report category boundaries when continuous variables were categorized	

		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	P12-13
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	P13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	P13-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	P15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	P15

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

The relationship between ambulatory blood pressure variability and enlarged perivascular spaces: a cross-sectional study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2016-015719.R1
Article Type:	Research
Date Submitted by the Author:	11-Apr-2017
Complete List of Authors:	Yang, Shuna; Beijing Chaoyang Hospital, Neurology Qin, Wei; Beijing Chaoyang Hospital, Neurology Yang, Lei; Beijing Chaoyang Hospital, Neurology Fan, Huimin; Beijing Chaoyang Hospital, Neurology Li, Yue; Beijing Chaoyang Hospital, Neurology Yin, Jiangmei; Beijing Chaoyang Hospital, Neurology Hu, Wenli; Neurology
Primary Subject Heading:	Neurology
Secondary Subject Heading:	Health services research
Keywords:	cerebral small vessel disease, enlarged perivascular spaces, Virchow-Robin spaces, blood pressure variability, ambulatory blood pressure monitoring

The relationship between ambulatory blood pressure variability and enlarged perivascular spaces: a cross-sectional study

Shuna Yang[1], Wei Qin[1], Lei Yang[1], Huimin Fan[1], Yue Li[1], Jiangmei Yin[1], Wenli Hu[1*]

1: Department of Neurology, Beijing Chaoyang Hospital, Capital Medical University, Beijing, China

*: Corresponding Author

Email: huwenli@sina.com, Telephone: +8601085231376, Fax: 011-86-10-65926388

Institution address: Beijing Chaoyang Hospital, No.8 South Gongti Road, Chaoyang District, Beijing, China

Abstract

Objectives: Recent studies reported that 24-hour ambulatory blood pressure variability (ABPV) was associated with lacunar infarction and white matter hyperintensities (WMH). However, the relationship between ABPV and enlarged perivascular spaces (EPVS) hasn't been investigated. So in the study, we aimed to investigate whether ABPV was associated with EPVS by 24-hour ambulatory blood pressure monitoring (ABPM).

Design: We conducted this study as a cross-sectional study.

Settings: The study was based on patients for physical examinations in our hospital from May 2013 to Jun 2016.

Participants: Patients with both brain MRI scans and 24-hour ABPM were included and patients with acute stroke, a history of severe stroke and some other severe diseases were excluded. A total of 573 Chinese were prospectively enrolled in this study.

Primary and secondary outcome measures: EPVS in basal ganglia (BG) and white matter (WM) were identified on MRI and classified into three categories by the severity. WMH were scored by Fazekas scale. Spearman correlation analysis and ordinal logistic regression analysis were used to determine the relationship between ABP levels and EPVS.

Results: There were statistical differences in all of the following ABPV metrics: standard deviation (SD) and coefficient of variation (CV) of systolic blood pressure (SBP), CV of diastolic blood pressure (DBP) in 24-hour, daytime and nighttime and SD of DBP in nighttime among the subgroups stratified by the severity of EPVS in BG. The above ABPV metrics were positively associated with the degree of EPVS in BG. The association between ABPV and EPVS in BG was unchanged after controlling for confounders. Spearman correlation analysis showed ABPV weren't related to the degree of EPVS in WM.

Conclusion: ABPV was independently associated with EPVS in BG after controlling for the blood pressure, but not in WM. Pathogenesis of EPVS in BG and WM might be different.

Keywords cerebral small vessel disease, enlarged perivascular spaces, Virchow-Robin spaces, blood pressure variability, ambulatory blood pressure monitoring

Strengths and limitations of this study

- Assessments of EPVS and WMH were performed by two experienced neurologists blinded to clinical information and disagreements were resolved by consensus, which ensure the accuracy of the assessments.
- Detailed information on some confounders crucial to the interpretation of EPVS was collected and ordinal logistic regression analysis was performed to determine the independency of association.
- The study was based on hospital physical examinations people in a single center and the cohort may not represent the general population.
- This was a cross-sectional study, and the causal relationship between ABPV and EPVS could not be established.

INTRODUCTION

Perivascular spaces, or Virchow-Robin spaces, are perivascular compartments surrounding the small penetrating cerebral vessels, serving as an important drainage system for interstitial fluid and solute in brain[1]. They can dilate with accumulation of the interstitial fluid[2, 3]. Enlarged perivascular spaces (EPVS) appear as punctate or linear signal intensities similar to cerebrospinal fluid (CSF) on all MRI sequences in white matter (WM), basal ganglia (BG), hippocampus and brainstem[4, 5]. Recent studies indicated that EPVS were a magnetic resonance imaging (MRI) marker of cerebral small vessel diseases (CSVD) and were associated with other morphological features of CSVD such as white matter hyperintensities (WMH) and lacunes[6, 7]. Some studies found EPVS were associated with impaired cognitive function[5], incident dementia[8] and sleep disorders[9]. Therefore, it is of clinical importance to understand the risk factors of EPVS and search for treatable methods.

24-hour ambulatory blood pressure monitoring (ABPM) is proven to be a more useful and scientific method to predict blood pressure-related brain damage than single office blood pressure measurements[10, 11]. Ambulatory blood pressure variability

(ABPV) could be well documented by 24-hour ABPM. Previous studies demonstrated higher ABPV increased the risk of cardiovascular events[12, 13], WMH, lacunar infarction, and cognitive decline[14, 15]. WMH, lacunar infarction and EPVS are all neuroimaging features of CSVD and share some risk factors, such as age and hypertension[16]. However, the relationship between ABPV and EPVS has never been investigated. So in the study, we aimed to investigate whether ABPV was independently associated with EPVS by 24-hour ABPM.

METHODS

Study subjects

We conducted this study as a cross-sectional study. The patients meeting both inclusion and exclusion criteria for physical examinations were prospectively enrolled to avoid selection bias in General Department or Neurology Department of Beijing Chaoyang Hospital Affiliated to Capital Medical University from May 2013 to Jun 2016. They were usual, mandatory and relatively healthy individuals in the Chinese population. The number of arriving patients during the study period, inclusion and exclusion criteria determined the sample size. Inclusion criteria were: (1) patients underwent both brain MRI scans and 24-hour ABPM within 1 month; (2) patients agreed to participate in our study and sign an informed consent. The following patients were excluded: (1) patients with acute stroke, Parkinson disease, dementia, severe traumatic or toxic or infectious brain injury, and brain tumor; (2) patients with severe heart disease, recent myocardial infarction or angina pectoris disorders, severe infections, severe nephrosis or liver disease, thrombotic diseases and tumor; (3) patients with history of severe ischemic (the largest diameter of infarct size＞20mm on diffusion-weighted imaging and fluid attenuated inversion recovery) or hemorrhagic stroke because of difficulty assessments on EPVS; (4) patients with invalid 24-hour ABPM data (The 24-h ABPM data were considered invalid if measurement was < 70%, < 1 measurement per hour during daytime, and < 6 in total during nighttime).

Assessments of EPVS and WMH

The neurological image examinations were performed in Radiology Department of

our hospital. MR imagines were acquired on a 3.0 T MR scanner (Siemens, Erlangen, Germany).

EPVS were defined as CSF-like signal intensity lesions of round, ovoid, or linear shape of <3mm and located in areas supplied by perforating arteries[6, 17]. We distinguished lacune from EPVS by their larger size (>3mm), spheroid shape and surrounding hyperintensities on FLAIR. WMH were defined as hyperintense signals on T2-weighted and FLAIR and decreased signal intensities on T1-weighted MR imaging.

EPVS in BG and WM were separately assessed according to the scales which were used in other studies[18, 19]. In BG, EPVS were rated according to the number in the slice containing the maximum amount of EPVS. The grades of EPVS were rated as follows: grade 1: < 5 EPVS, grade 2: 5 to 10 EPVS, grade 3: > 10 but still countable, and grade 4: infinite number of EPVS. In WM, EPVS were scored as follows: grade 1：<10 EPVS in total WM, grade 2：>10 in total WM and <10 in the slice containing the maximum number of EPVS, grade 3：10 to 20 EPVS in the slice containing the maximum number of EPVS, grade 4：> 20 in the slice containing the maximum number of EPVS. We classified EPVS into three categories: degree 1 = grade 1; degree 2 = grade 2; degree 3 = grade 3 or 4.

WMH were scored by Fazekas scale. The detailed description of assessment has been previously published[20]. Periventricular and deep WMH were evaluated separately and totaled together as Fazekas scores.

The intrarater agreement for the rating of EPVS and WMH was assessed on a random sample of 100 individuals with a month interval between the first and second readings. Assessments of EPVS and WMH were performed by two experienced neurologists blinded to clinical information to avoid bias. Random scans of 100 individuals were independently examined by the two experienced neurologists blinded to each other's readings. The *k* statistics of intrarater and interrater agreement was 0.80 or above, indicating good reliability. Disagreement was resolved by discussing with other co-authors.

24-hour ambulatory blood pressure monitoring

24-hour ABPM was performed using an automated system (FB-250; Fukuda Denshi, Tokyo, Japan). BP was measured every 30 minutes during the daytime (8:00 AM to 11:00 PM) and every 60 minutes during the nighttime (11:00 PM to 8:00 AM). We excluded a 2-hour transition period around the reported rising and retiring times. The mean systolic blood pressure (SBP), diastolic blood pressure (DBP), coefficient of variation (CV) and standard deviation (SD) of SBP and DBP during 24-hour, daytime, and nighttime were collected. The CV value was defined as the ratio between the SD and the mean SBP or DBP at the same periods. SD and CV were considered as metrics of BPV in this study. Patients continued their previous medication, and we registered the use of anti-hypertension drugs.

Statistical analysis

Continuous variables were presented as mean values ± SD and compared with ANOVA for factors with a normal distribution, whereas no normally distributed variables were compared with Kruskal–Wallis test as appropriate. Categorical variables were expressed as percentages and compared using the chi-square test. Spearman correlation analysis was used to calculate the association between ABPV and the severity of EPVS. In addition, ordinal logistic regression analysis was performed to determine whether the ABPV were independently associated with EPVS after adjustment for other confounders. The results were based on valid data; missing data were excluded. Analyses were performed with Statistical Package for Social Sciences (SPSS version21.0), and statistical significance was accepted at the $p < 0.05$.

RESULTS

Baseline characteristics of the study participants

742 patients underwent both brain MRI scans and 24-hour ABPM within 1 month in Medical Care Department or Neurology Department of our hospital from May 2013 to Jun 2016. 40 patients were excluded because of acute stroke, 21 were excluded because of history of severe or hemorrhagic stroke, 15 were excluded because of a history of tumor and 93 were excluded because of invalid ABPM data, leaving 573 patients for the present study. None of them had missing data. There were no

statistical differences (P＞0.05) in age, body mass index, proportion of male, current smoking, current alcohol, diabetes, hypertension, coronary artery atherosclerosis disease and using of anti-hypertensive drugs between the excluded subjects and the final group (Supplementary file). Table 1 showed the characteristics of all enrolled subjects and subgroups stratified by the degree of EPVS in different brain regions. Age, Fazekas scale, proportion of hypertension and stroke/TIA, levels of blood urea nitrogen and creatinine increased with the degree of EPVS in BG increasing. There were statistical differences in age, Fazekas scale and proportion of coronary artery atherosclerosis disease (CAD) among subgroups based on the degree of EPVS in WM.

There were statistical differences in the mean SBP of 24-hour, daytime, and nighttime among the categories stratified by the degree of EPVS in BG. The results of spearman correlation analysis showed SBP was positively related to higher degree of EPVS in BG during all periods (SBP of 24-hour: r=0.23, p < 0.01; SBP of daytime: r=0.25, p < 0.01; SBP of nighttime: r=0.30, p < 0.01). The mean DBP of daytime and nighttime increased with the degree of EPVS in WMH increasing. However, the results of spearman correlation analysis showed that DBP levels were not associated with higher numbers of EPVS in CSO (p > 0.05).

Table 1. General characteristics of all enrolled subjects and subgroups stratified by the severity of EPVS

Characteristics	All patients	EPVS in BG			EPVS in WM		
		Degree 1	Degree 2	Degree 3	Degree 1	Degree 2	Degree 3
n (%)	573	244 (42.6%)	179 (31.2%)	150 (26.2%)	200 (34.9%)	207 (36.1%)	166 (29.0%)
Age, years	67.8±14.8	61.4±14.4**	67.6±13.8**	78.3±9.6**	70.45±15.2**	66.25±14.4**	66.46±14.3**
Sex, male (%)	355 (62.0)	143 (58.6)	108 (60.3)	104 (69.3)	115 (57.5)	128 (61.8)	112 (67.5)
Current smoking (%)	162 (28.3)	83 (34.0)*	61(34.1)*	18(12.0)*	52 (26.0)	60 (29.0)	50 (30.1)
Current alcohol (%)	126 (22.0)	62 (25.4)*	45 (25.1)*	19 (12.7)*	36 (18.0)	50 (24.2)	40 (24.1)
Hypertension (%)	420 (73.3)	170 (69.7)*	122 (68.2)*	128 (85.3)*	150 (75.0)	145 (70.5)	125 (74.7)
Diabetes (%)	191 (33.3)	78 (32.0)	59 (33.0)	54 (36.0)	71 (35.5)	62 (30.0)	58 (34.9)

CAD (%)	140 (24.4)	48 (19.7)	48 (26.8)	44 (29.3)	61 (30.5) *	45 (21.7) *	34 (20.5) *
Stroke or TIA (%)	125 (21.8)	40 (16.4)**	33 (18.4)**	52 (34.7)**	49 (24.5)	39 (18.8)	37 (22.2)
BMI, kg/m^2	25.6±3.5	25.6±3.4	25.3±3.5	25.8±3.5	25.8±3.4	25.4±3.5	25.5±3.5
HDL, mmol/L	1.2±0.4	1.2±0.4	1.2±0.4	1.2±0.3	1.2±0.4	1.2±0.4	1.2±0.3
LDL, mmol/L	2.5±0.8	2.5±0.8	2.5±0.8	2.3±08	2.4±0.8	2.4±0.8	2.5±0.7
HbA1, %	6.4±1.3	6.4±1.3	6.4±1.4	6.5±1.2	6.4±1.1	6.5±1.4	6.5±1.4
BUN, mmol/L	5.8±2.1	5.5±1.7**	5.9±2.6**	6.3±2.0**	6.0±2.5	5.7±1.9	5.8±1.9
Creatinine, umol/L	79.1±27.1	74.0±19.3**	81.7±32.6**	84.2±29.4**	81.2±27.4	77.7±27.3	78.3±26.4
Fazekas scale	3.1±1.8	2.2±1.4**	3.1±1.7**	4.7±1.5**	3.5±2.0**	2.9±1.7**	3.1±1.7**
Using of anti-hypertensive drugs (%)	342 (59.7)	130 (53.3) *	96 (53.6) *	116 (77.3) *	129 (64.5)	114 (55.1)	99 (59.6)
Class of anti-hypertensive drugs							
Dihydropyridinic CCB (%)	226 (39.4)	74 (30.3)	67 (37.4)	63 (42.0)	69 (34.5)	79 (38.2)	55 (33.1)
ACEI (%)	26 (4.5)	11 (4.5)	6 (3.4)	9 (6.0)	8 (4.0)	9 (4.3)	9 (5.7)
ARB (%)	160 (27.9)	70 (28.7)	46 (25.7)	44 (29.3)	69 (34.5) *	52 (25.1) *	39 (23.5) *
β-Blockers (%)	96 (16.8)	34 (13.9)	28 (15.6)	34 (22.7)	40 (20.0)	31 (15.0)	25 (15.1)
Nonloop diuretics (%)	39 (6.8)	20 (8.2)	12 (6.7)	7 (4.7)	16 (8.0)	13 (6.3)	10 (6.0)
24-hour							
SBP (mmHg)	133±16.4	129±15.6**	134±16.0**	138±16.5**	133±16.5	132±17.1	132.9±15.4
DBP (mmHg)	76±9.6	77±9.5	76±10.0	75±9.1	75±9.5*	76±9.6*	77±9.6*
Daytime							
SBP (mmHg)	135±16.6	130±16.0**	135±16.0**	141±16.4**	135±16.6	134±17.6	135±15.3
DBP (mmHg)	77±10.0	77±10.0*	77±10.3*	75±9.5*	75±9.9*	77±10.1*	78±9.9*
Nighttime							
SBP (mmHg)	129±19.8	123±18.5**	131±18.9**	137±19.9**	130±20.8	128±19.5	129±19.0
DBP (mmHg)	74±10.7	74±10.5	73±11.2	74±10.4	723±10.8	74±10.5	75±10.8

EPVS, enlarged perivascular spaces; BG, basal ganglia; WM, white matter; BMI, body mass index; CAD, coronary artery atherosclerosis disease; TIA, transient ischemic attack; HDL, high-density lipoprotein; LDL, low-density lipoprotein; HbA1c, hemoglobin A1c; BUN, blood urea nitrogen, CCB, calcium-channel blocker;

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker. * $p < 0.05$, * * $p < 0.01$.

Association between ABPV and EPVS in BG

SD and CV of ambulatory blood pressure in different categories stratified by the degree of EPVS in BG were presented in Table 2. There were statistical differences ($p < 0.05$) in all of the following BPV metrics: SD and CV of SBP, CV of DBP during 24-hour, daytime and nighttime and SD of DBP during nighttime among the three subgroups stratified by the severity of EPVS in BG. Theses metrics gradually increased with the degree of EPVS increasing (Fig 1-3). The results of spearman correlation analysis demonstrated theses metrics were positively associated with the degree of EPVS in BG ($r>0$, $P<0.05$) (Table 3). The association between ABPV and EPVS were unchanged after controlling for demographic confounders (model 1), Fazekas scale (model 2) and the mean SBP or DBP during the same period (model 3), which indicated that the ABPV were independently associated with EPVS in BG. The results of ordinal logistic regression analysis were presented in Table 4.

Association between ABP Levels and EPVS in WM

SD and CV of ambulatory blood pressure in different categories stratified by degree of EPVS in WM were also presented in Table 2. There were statistical differences ($p < 0.05$) in SD of SBP, CV of SBP, SD of DBP and CV of DBP during 24-hour and daytime among the three categories. However, there were not linear trend among the three subgroups. The results of spearman correlation analysis showed there were no linear correlation between theses metrics and the degree of EPVS in WM (Table 3).

Table 2. Results of ABPV in all subjects and subgroups stratified by the severity of EPVS

	All patietns	EPVS in BG				EPVS in WM			
		Degree 1	Degree 2	Degree 3	P	Degree 1	Degree 2	Degree 3	P
24-hour									
SD of SBP, mmHg	18.28±5.27	16.93±4.76	18.57±4.56	20.13±6.21	＜0.001	18.86±5.56	17.36±5.11	18.73±4.99	0.004

SD of DBP, mmHg	12.56±3.58	12.22±3.56	12.62±3.34	13.05±3.86	0.149	12.83±3.76	11.85±3.32	13.14±3.56	0.001
CV of SBP, %	13.83±3.80	13.21±3.56	13.99±3.54	14.64±4.26	0.004	14.16±3.87	13.23±3.70	14.18±3.76	0.028
CV of DBP, %	16.68±4.74	16.03±4.68	16.82±4.46	17.55±5.04	0.013	17.22±4.76	15.78±4.72	17.14±4.60	0.001
Daytime									
SD of SBP, mmHg	18.02±5.70	16.66±4.93	18.21±5.35	19.99±6.65	＜0.001	18.68±5.98	16.99±5.47	18.50±5.49	0.004
SD of DBP, mmHg	12.56±4.01	12.25±3.80	12.51±3.93	13.12±4.40	0.241	12.81±4.06	11.76±3.71	13.26±4.17	0.001
CV of SBP, %	13.45±4.08	12.84±3.75	13.62±4.14	14.26±4.38	0.005	13.86±4.16	12.76±3.88	13.81±4.12	0.016
CV of DBP, %	16.48±5.19	15.84±4.77	16.47±5.24	17.54±5.63	0.024	16.98±4.88	15.47±5.12	17.15±5.48	0.002
Nighttime									
SD of SBP, mmHg	15.21±7.37	13.79±7.71	15.18±5.74	17.54±7.97	＜0.001	15.08±6.09	14.94±8.66	15.69±7.05	0.180
SD of DBP, mmHg	10.43±4.50	9.81±4.33	10.77±4.55	11.03±4.61	0.010	10.23±4.11	10.26±4.58	10.88±4.84	0.247
CV of SBP, %	11.85±5.37	11.22±5.53	11.77±4.56	12.95±5.84	0.005	11.69±4.62	11.70±5.95	12.23±5.48	0.411
CV of DBP, %	14.26±6.02	13.42±5.88	14.75±5.89	15.03±628	0.003	14.20±5.61	14.08±6.30	14.54±6.17	0.426

1 SBP: systolic blood pressure; DBP: diastolic blood pressure; CV: coefficient of
2 variation; SD: standard deviation.

3 **Table 3.** Results of spearman correlation analysis between the degree of EPVS and
4 ABPV

	EPVS in BG		EPVS in WM	
	r	P value	r	P value
24h				
SD of SBP	0.216	0.000	-0.013	0.762
SD of DBP	0.082	0.051	0.030	0.481
CV of SBP	0.137	0.001	-0.008	0.854
CV of DBP	0.123	0.003	-0.028	0.505
Daytime				

SD of SBP	0.205	0.000	-0.024	0.562
SD of DBP	0.065	0.120	0.031	0.459
CV of SBP	0.135	0.001	-0.023	0.585
CV of DBP	0.109	0.009	-0.017	0.679
Nighttime				
SD of SBP	0.229	0.000	0.020	0.637
SD of DBP	0.125	0.003	0.043	0.309
CV of SBP	0.136	0.001	0.027	0.521
CV of DBP	0.135	0.001	0.007	0.870

SBP: systolic blood pressure; DBP: diastolic blood pressure; CV: coefficient of variation; SD: standard deviation.

Table 4. Results of ordinal logistic regression analysis between ABPV and EPVS in BG

	Model 1		Model 2		Model 3	
	Odds ratio (95% CI)	P	Odds ratio (95% CI)	P	Odds ratio (95% CI)	P
24h						
SD of SBP	1.55 (1.32-1.83)	＜0.001	1.48 (1.25-1.75)	＜0.001	1.41 (1.19-1.68)	＜0.001
CV of SBP	1.47 (1.19-1.83)	＜0.001	1.48 (1.18-1.85)	0.001	1.60 (1.27-2.02)	＜0.001
CV of DBP	1.59 (1.13-2.24)	0.008	1.69 (1.18-2.42)	0.004	1.81 (1.25-2.60)	0.001
Daytime						
SD of SBP	1.44 (1.25-1.67)	＜0.001	1.39 (1.19-1.61)	＜0.001	1.31 (1.12-1.54)	0.001
CV of SBP	1.32 (1.08-1.61)	0.006	1.32 (1.08-1.62)	0.008	1.43 (1.16-1.77)	0.001
CV of DBP	1.49 (1.10-2.04)	0.011	1.59 (1.15-2.19)	0.005	1.67 (1.21-2.31)	0.002
Nighttime						
SD of SBP	1.29 (1.15-1.46)	＜0.001	1.25 (1.11-1.40)	＜0.001	1.21 (1.07-1.37)	0.002
SD of DBP	1.39 (1.15-1.67)	＜0.001	1.33 (1.11-1.61)	0.003	1.31 (1.12-1.54)	0.001
CV of SBP	1.27 (1.09-1.48)	0.002	1.26 (1.08-1.47)	0.003	1.31 (1.08-1.58)	0.006
CV of DBP	1.19 (1.04-1.36)	0.013	1.20 (1.04-1.37)	0.012	1.21 (1.05-1.39)	0.008

Results of ordinal regression analysis presented as OR per 5% increase in CV of

blood pressure and 5 mmHg in SD of blood pressure.

Model1: adjusted for age, smoking, alcohol, hypertension, stroke/TIA, BUN, creatinine and using of anti-hypertensive drugs.

Model2: model 1 + Fazekas scale.

Model3: model 2 + the mean SBP or DBP during the same period.

DISCUSSION

In this study, we explored the relationship between ABPV and EPVS based on hospital physical examinations population. Our data suggested that all of the following metrics: SD of SBP, CV of SBP and CV of DBP during 24-hour, daytime and nighttime and SD of DBP during nighttime were positively associated with the degree of EPVS in BG. The association between the above ABPV metrics and EPVS in BG were unchanged after controlling for demographic confounders, Fazekas scale and the mean SBP or DBP during the same period. Although there were statistical differences ABPV metrics in 24-hour and daytime among the three subgroups stratified by EPVS severity in WM, there were not linear correlation between ABPV and the degree of EPVS in WM. In addition, we found age, Fazekas scale, hypertension, stroke/transient ischemic attack (TIA), levels of blood urea nitrogen and creatinine were positively associated with the degree of EPVS in BG.

There were methodological strengths of our study. We recruited participants strictly according to inclusion and exclusion criteria to avoid selection bias. The patients with acute cerebrovascular and cardiovascular disorders were excluded to avoid the impact of the acute stroke, recent myocardial infarction or angina pectoris on blood pressure. The patients with history of severe ischemic (the largest diameter of infarct size＞20mm on diffusion-weighted imaging and fluid attenuated inversion recovery) or hemorrhagic stroke were exclude because of difficulty and inaccurate assessments on EPVS. In addition, assessments of EPVS and WMH were performed by two experienced neurologists blinded to clinical information and disagreements were resolved by consensus, which ensure the accuracy of the assessments. We collected detailed information on vascular confounders, WMH, levels of blood urea nitrogen and creatinine, which are crucial to the interpretation of EPVS[6, 21]. So we think the

reliability of the data is high. There were some limitations in our study. First, our study was based on hospital physical examinations people in a single center and the cohort may not represent the general population. According to our observation, these people had a higher material standard of living than the general population in China, and some of them showed more anxiety symptoms. But it's regrettable that we didn't assess the anxiety symptoms by the Hamilton Anxiety Rating Scale and didn't collect the patients' education level. Second, this was a cross-sectional study, and the causal relationship between ABPV and EPVS could not be established. Third, all participants underwent 24-hour ABPM which could only show short-term ABPV. It has been demonstrated that the prognostic significance of BPV on vascular diseases is weaker for short-term than for long-term BPV[22].

This is the first study to investigate the relationship between ABPV and EPVS. Previously, several studies investigated the relationship between EPVS and hypertension. In a prospective, multicenter, hospital-based study, Zhang CQ et al[19] found hypertension was associated with the severity of EPVS in WM, not in BG. Klarenbeek P et al[23] investigated the association between ABP levels and EPVS in first-ever lacunar stroke patients. They found higher day systolic, day diastolic and 24-hour diastolic BP levels were independently associated EPVS in BG, and no relation between ABP levels and EPVS in WM. We also analyzed the correlation between ABP levels and EPVS. We found ABP levels were associated with EPVS in BG, but not in WMH, which is in agreement with Klarenbeek P et al.'s study. However, we found only SBP was positively related to higher degree of EPVS in BG in all periods, and no relation between DBP and EPVS, which are different form previous results. The different study population and different scoring methods of assessing EPVS may partly lead to the different results. Our data suggested that SD of SBP, CV of SBP and CV of DBP in all periods were positively associated with the degree of EPVS in BG, but not in WM. The present study couldn't explain the phenomenon. This may be caused by different pathogenesis of EPVS at the different locations[18, 19, 24]. Previous studies have found the anatomical structure of EPVS located in BG and WM were different[25]. The arteries in the basal ganglia are

surrounded by 2 distinct coats of leptomeninges separated by a perivascular space which is continuous with the perivascular space around arteries in the subarachnoid space. Whereas there are only single periarterial layer of leptomeninges surrounding the arteries in the cerebral cortex and they penetrate into the white matter. Drainage of interstitial fluid from the brain to cervical lymph nodes may be mainly along perivascular spaces in WM rather than in BG[3, 26]. In addition, the effect of age, hypertension on EPVS seems to be stronger for EPVS located in BG than for those located in WM[18]. Similarly, the association between EPVS and the load of WMH, taken as a marker of CSVD, also appears to be stronger in BG than in WM. Thus, their dilation may present differences in terms of risk factors as well as in mechanisms in BG and WM. However, the reason why SBP related differently in these two locations remains unclear because there are a very limited number of studies on mechanisms underlying dilation of perivascular spaces in BG and WM. Several studies have demonstrated higher ABPV increased the risk of neuroimaging features of CSVD, such as WMH and lacunar infarction[14, 15]. Our results found higher ABPV was independently with higher degree of EPVS in BG, which support the notion that EPVS in BG are a separate marker of CSVD.

An increased permeability of the small vessel walls and blood brain barrier (BBB) are considered to contribute to the development of EPVS, which has been reported to be associated with damage of microvascular endothelial cells and their tight junctions[1, 16, 27]. Higher ABPV would lead to more mechanical stress on the wall vessel, endothelial injury[28] and arterial stiffness[29]. So, it is reasonable that high ABPV contribute to the development of EPVS by the damage to endothelial cell. Our results may remind clinicians that they should pay attention to patients' ABPV and lower patients' ABPV in their clinical work. In the future, the causal relationship between ABPV and EPVS should be established in a prospective cohort study. And the relationship between ABPV and EPVS should be explored.

CONCLUSION

SD of SBP, CV of SBP and CV of DBP during all periods and SD of DBP during nighttime were positively associated with the degree of EPVS in BG. The association

was unchanged after controlling for confounders. No relation was found between ABPV and EPVS in WM. It is important for clinicians to reduce both patients' high blood pressure levels and ABPV.

Contributors WH conceived and designed the experiments. SY, WQ, LY and HF participated in the data collection. JY and YL participated in the analysis of the data. SY drafted the manuscript. WH has given final approval of the version to be published. All authors read and approved the final manuscript.

Funding This work is supported by National Natural Science Foundation of China (Grant No. 81271309).

Conflict of Interest None declared.

Ethic approval The study was approved by the Ethics Committee of Beijing Chaoyang Hospital Affiliated to Capital Medical University and was performed in accordance with the declaration of Helsinki.

Acknowledgements

The authors thank all the study participants.

Data sharing statement No additional data are available.

Reference

1. Kwee RM, Kwee TC. Virchow-robin spaces at mr imaging. *Radiographics : a review publication of the Radiological Society of North America, Inc*. 2007;27:1071-1086
2. Ozturk MH, Aydingoz U. Comparison of mr signal intensities of cerebral perivascular (virchow-robin) and subarachnoid spaces. *Journal of computer assisted tomography*. 2002;26:902-904
3. Abbott NJ. Evidence for bulk flow of brain interstitial fluid: Significance for physiology and pathology. *Neurochemistry international*. 2004;45:545-552
4. Zhu YC, Dufouil C, Mazoyer B, Soumare A, Ricolfi F, Tzourio C, Chabriat H. Frequency and location of dilated virchow-robin spaces in elderly people: A population-based 3d mr imaging study. *AJNR. American journal of neuroradiology*. 2011;32:709-713
5. Maclullich AM, Wardlaw JM, Ferguson KJ, Starr JM, Seckl JR, Deary IJ. Enlarged perivascular spaces are associated with cognitive function in healthy elderly men. *Journal of neurology, neurosurgery, and psychiatry*. 2004;75:1519-1523
6. Wardlaw JM, Smith EE, Biessels GJ, Cordonnier C, Fazekas F, Frayne R, Lindley RI, O'Brien JT, Barkhof F, Benavente OR, Black SE, Brayne C, Breteler M, Chabriat H, Decarli C, de Leeuw FE, Doubal F, Duering M, Fox NC, Greenberg S, Hachinski V, Kilimann I, Mok V, Oostenbrugge R, Pantoni L, Speck O, Stephan BC, Teipel S, Viswanathan A, Werring D, Chen C, Smith C, van Buchem M, Norrving B, Gorelick PB, Dichgans M. Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration.

The Lancet. Neurology. 2013;12:822-838

7. Doubal FN, MacLullich AM, Ferguson KJ, Dennis MS, Wardlaw JM. Enlarged perivascular spaces on mri are a feature of cerebral small vessel disease. *Stroke*. 2010;41:450-454
8. Zhu YC, Dufouil C, Soumare A, Mazoyer B, Chabriat H, Tzourio C. High degree of dilated virchow-robin spaces on mri is associated with increased risk of dementia. *Journal of Alzheimer's disease : JAD*. 2010;22:663-672
9. Berezuk C, Ramirez J, Gao F, Scott CJ, Huroy M, Swartz RH, Murray BJ, Black SE, Boulos MI. Virchow-robin spaces: Correlations with polysomnography-derived sleep parameters. *Sleep*. 2015;38:853-858
10. Ohkubo T, Hozawa A, Nagai K, Kikuya M, Tsuji I, Ito S, Satoh H, Hisamichi S, Imai Y. Prediction of stroke by ambulatory blood pressure monitoring versus screening blood pressure measurements in a general population: The ohasama study. *Journal of hypertension*. 2000;18:847-854
11. Shimada K, Kawamoto A, Matsubayashi K, Ozawa T. Silent cerebrovascular disease in the elderly. Correlation with ambulatory pressure. *Hypertension (Dallas, Tex. : 1979)*. 1990;16:692-699
12. Conen D, Bamberg F. Noninvasive 24-h ambulatory blood pressure and cardiovascular disease: A systematic review and meta-analysis. *Journal of hypertension*. 2008;26:1290-1299
13. Rothwell PM. Does blood pressure variability modulate cardiovascular risk? *Current hypertension reports*. 2011;13:177-186
14. Yamaguchi Y, Wada M, Sato H, Nagasawa H, Koyama S, Takahashi Y, Kawanami T, Kato T. Impact of ambulatory blood pressure variability on cerebral small vessel disease progression and cognitive decline in community-based elderly japanese. *American journal of hypertension*. 2014;27:1257-1267
15. Filomena J, Riba-Llena I, Vinyoles E, Tovar JL, Mundet X, Castane X, Vilar A, Lopez-Rueda A, Jimenez-Balado J, Cartanya A, Montaner J, Delgado P. Short-term blood pressure variability relates to the presence of subclinical brain small vessel disease in primary hypertension. *Hypertension (Dallas, Tex. : 1979)*. 2015;66:634-640; discussion 445
16. Wardlaw JM, Smith C, Dichgans M. Mechanisms of sporadic cerebral small vessel disease: Insights from neuroimaging. *The Lancet. Neurology*. 2013;12:483-497
17. Groeschel S, Chong WK, Surtees R, Hanefeld F. Virchow-robin spaces on magnetic resonance images: Normative data, their dilatation, and a review of the literature. *Neuroradiology*. 2006;48:745-754
18. Zhu YC, Tzourio C, Soumare A, Mazoyer B, Dufouil C, Chabriat H. Severity of dilated virchow-robin spaces is associated with age, blood pressure, and mri markers of small vessel disease: A population-based study. *Stroke*. 2010;41:2483-2490
19. Zhang C, Chen Q, Wang Y, Zhao X, Wang C, Liu L, Pu Y, Zou X, Du W, Pan Y, Li Z, Jing J, Wang D, Luo Y, Wong KS. Risk factors of dilated virchow-robin spaces are different in various brain regions. *PloS one*. 2014;9:e105505
20. Fazekas F, Chawluk JB, Alavi A, Hurtig HI, Zimmerman RA. Mr signal abnormalities at 1.5 t in alzheimer's dementia and normal aging. *AJR. American journal of roentgenology*. 1987;149:351-356
21. Yamamoto Y, Ohara T, Nagakane Y, Tanaka E, Morii F, Koizumi T, Akiguchi I. Chronic kidney disease, 24-h blood pressure and small vessel diseases are independently associated

with cognitive impairment in lacunar infarct patients. *Hypertension research : official journal of the Japanese Society of Hypertension*. 2011;34:1276-1282

22. Rothwell PM, Howard SC, Dolan E, O'Brien E, Dobson JE, Dahlof B, Sever PS, Poulter NR. Prognostic significance of visit-to-visit variability, maximum systolic blood pressure, and episodic hypertension. *Lancet (London, England)*. 2010;375:895-905

23. Klarenbeek P, van Oostenbrugge RJ, Lodder J, Rouhl RP, Knottnerus IL, Staals J. Higher ambulatory blood pressure relates to enlarged virchow-robin spaces in first-ever lacunar stroke patients. *Journal of neurology*. 2013;260:115-121

24. Satizabal CL, Zhu YC, Dufouil C, Tzourio C. Inflammatory proteins and the severity of dilated virchow-robin spaces in the elderly. *Journal of Alzheimer's disease : JAD*. 2013;33:323-328

25. Pollock H, Hutchings M, Weller RO, Zhang ET. Perivascular spaces in the basal ganglia of the human brain: Their relationship to lacunes. *Journal of anatomy*. 1997;191 (Pt 3):337-346

26. Weller RO, Subash M, Preston SD, Mazanti I, Carare RO. Perivascular drainage of amyloid-beta peptides from the brain and its failure in cerebral amyloid angiopathy and alzheimer's disease. *Brain pathology (Zurich, Switzerland)*. 2008;18:253-266

27. Wuerfel J, Haertle M, Waiczies H, Tysiak E, Bechmann I, Wernecke KD, Zipp F, Paul F. Perivascular spaces--mri marker of inflammatory activity in the brain? *Brain : a journal of neurology*. 2008;131:2332-2340

28. Diaz KM, Veerabhadrappa P, Kashem MA, Thakkar SR, Feairheller DL, Sturgeon KM, Ling C, Williamson ST, Kretzschmar J, Lee H, Grimm H, Babbitt DM, Vin C, Fan X, Crabbe DL, Brown MD. Visit-to-visit and 24-h blood pressure variability: Association with endothelial and smooth muscle function in african americans. *Journal of human hypertension*. 2013;27:671-677

29. Schillaci G, Bilo G, Pucci G, Laurent S, Macquin-Mavier I, Boutouyrie P, Battista F, Settimi L, Desamericq G, Dolbeau G, Faini A, Salvi P, Mannarino E, Parati G. Relationship between short-term blood pressure variability and large-artery stiffness in human hypertension: Findings from 2 large databases. *Hypertension (Dallas, Tex. : 1979)*. 2012;60:369-377

Figure 1. The ABPV metrics of subgroups stratified by EPVS severity in BG during 24-hour. (a) CV of systolic blood pressure. (b) CV of diastolic blood pressure. (c) SD of systolic blood pressure. (d) SD of diastolic blood pressure.

Figure 2. The ABPV metrics of subgroups stratified by EPVS severity in BG during daytime. (a) CV of systolic blood pressure. (b) CV of diastolic blood pressure. (c) SD of systolic blood pressure. (d) SD of diastolic blood pressure.

Figure 3. The ABPV metrics of subgroups stratified by EPVS severity in BG during nighttime. (a) CV of systolic blood pressure. (b) CV of diastolic blood pressure. (c) SD of systolic blood pressure. (d) SD of diastolic blood pressure.

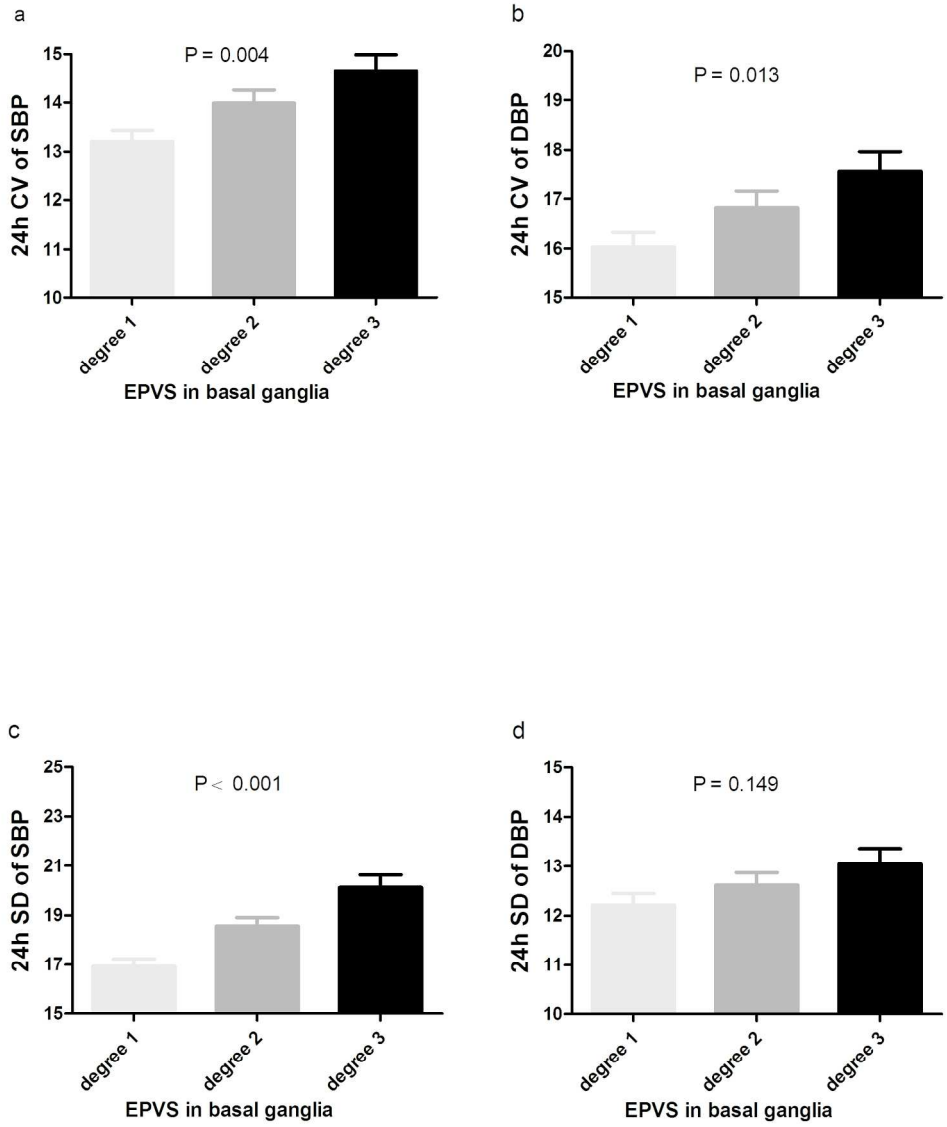


Figure 1. The ABPV metrics of subgroups stratified by EPVS severity in BG during 24-hour. (a) CV of systolic blood pressure. (b) CV of diastolic blood pressure. (c) SD of systolic blood pressure. (d) SD of diastolic blood pressure.

191x228mm (300 x 300 DPI)

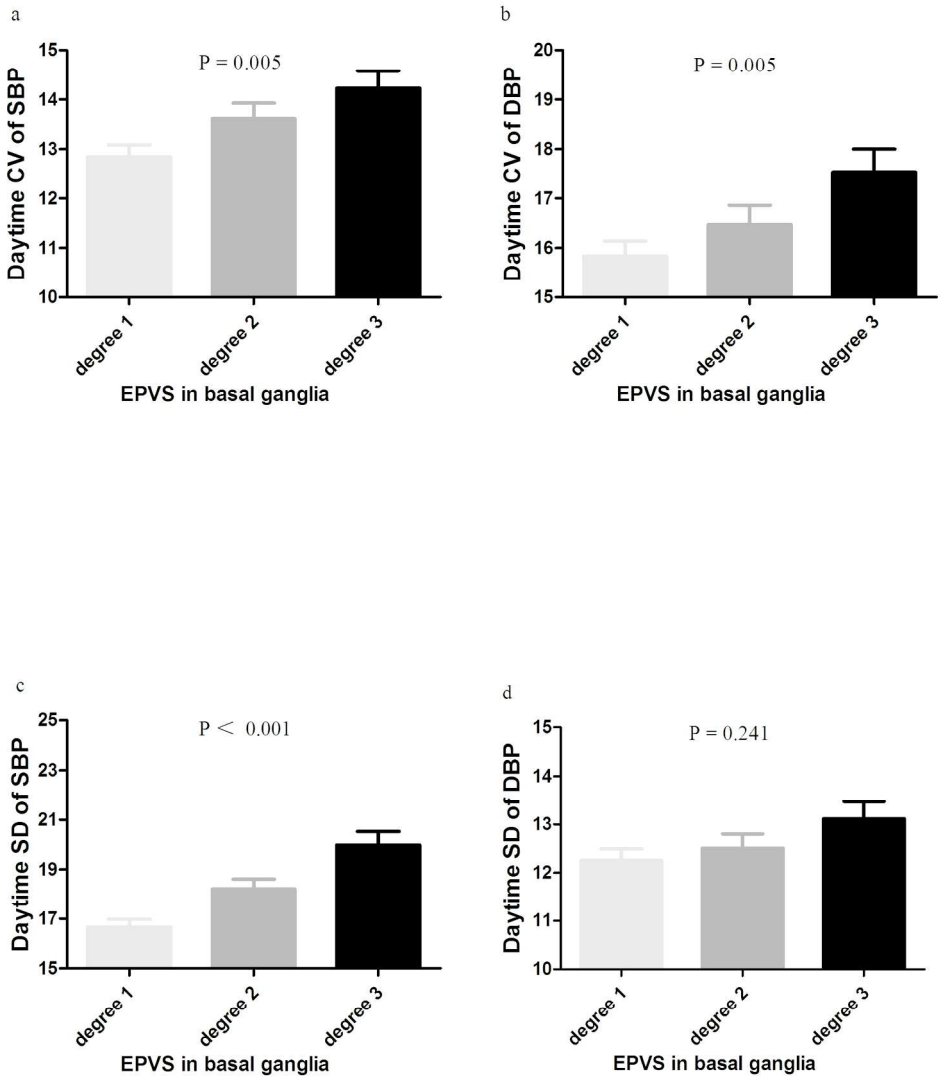


Figure 2. The ABPV metrics of subgroups stratified by EPVS severity in BG during daytime. (a) CV of systolic blood pressure. (b) CV of diastolic blood pressure. (c) SD of systolic blood pressure. (d) SD of diastolic blood pressure.

190x218mm (300 x 300 DPI)

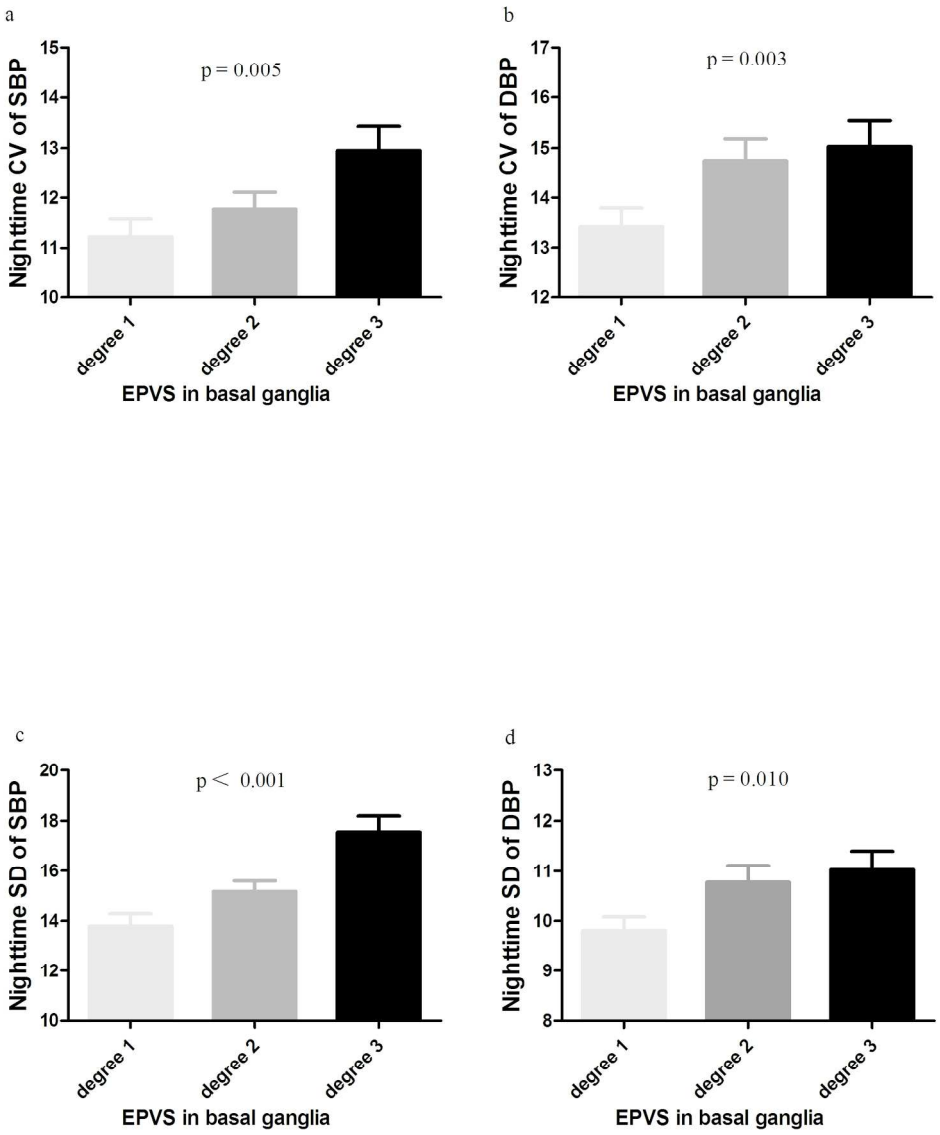
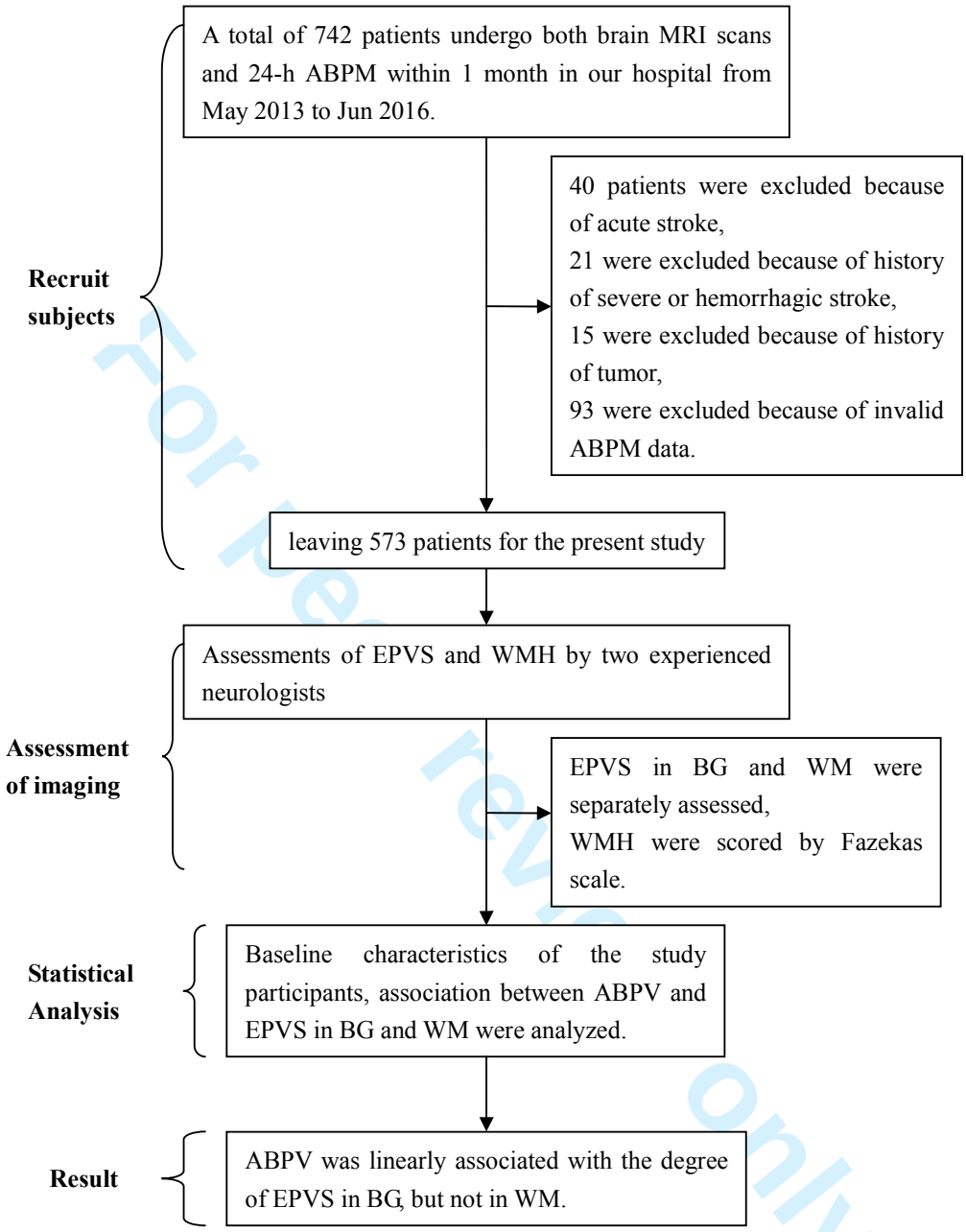


Figure 3. The ABPV metrics of subgroups stratified by EPVS severity in BG during nighttime. (a) CV of systolic blood pressure. (b) CV of diastolic blood pressure. (c) SD of systolic blood pressure. (d) SD of diastolic blood pressure.

189x227mm (300 x 300 DPI)

The comparison of general clinical characteristics between the included and excluded participants

Characteristics	enrolled patients	excluded patients	P
n	573	169	-
Age, years	67.8±14.8	69.6±9.6	0.443
Sex, male (%)	355 (62.0)	101(59.8)	0.607
Current smoking (%)	162 (28.3)	55(32.5)	0.283
Current alcohol (%)	126 (22.0)	42(24.9)	0.435
Hypertension (%)	420 (73.3)	115(68.0)	0.181
Diabetes (%)	191 (33.3)	44(26.0)	0.073
coronary atherosclerosis disease (%)	140 (24.4)	35(20.7)	0.316
body mass index, kg/m^2	25.6±3.5	25.1±3.0	0.160
Using of anti-hypertensive drugs (%)	342 (59.7)	99(58.6)	0.797



ABPM, ambulatory blood pressure monitoring; EPVS, enlarged perivascular spaces; WMH, white matter hyperintensities; BG, basal ganglia; WM, white matter.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	P1 and 2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	P2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	P3-4
Objectives	3	State specific objectives, including any prespecified hypotheses	P4
Methods			
Study design	4	Present key elements of study design early in the paper	P4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	P4
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	P4
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	P5-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	P5-6
Bias	9	Describe any efforts to address potential sources of bias	P4 and 5

Study size	10	Explain how the study size was arrived at	P4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	P6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	P6
		(*b*) Describe any methods used to examine subgroups and interactions	P6
		(*c*) Explain how missing data were addressed	P6
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	P6
		(b) Give reasons for non-participation at each stage	P6
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	P7
		(b) Indicate number of participants with missing data for each variable of interest	P7
Outcome data	15*	Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	P6-12
		(*b*) Report category boundaries when continuous variables were categorized	

		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	P12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	P12-13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	P13-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	P14-15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	P15

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

The relationship between ambulatory blood pressure variability and enlarged perivascular spaces: a cross-sectional study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2016-015719.R2
Article Type:	Research
Date Submitted by the Author:	16-May-2017
Complete List of Authors:	Yang, Shuna; Beijing Chaoyang Hospital, Neurology Qin, Wei; Beijing Chaoyang Hospital, Neurology Yang, Lei; Beijing Chaoyang Hospital, Neurology Fan, Huimin; Beijing Chaoyang Hospital, Neurology Li, Yue; Beijing Chaoyang Hospital, Neurology Yin, Jiangmei; Beijing Chaoyang Hospital, Neurology Hu, Wenli; Neurology
Primary Subject Heading:	Neurology
Secondary Subject Heading:	Health services research, Neurology
Keywords:	cerebral small vessel disease, enlarged perivascular spaces, Virchow-Robin spaces, blood pressure variability, ambulatory blood pressure monitoring

The relationship between ambulatory blood pressure variability and enlarged perivascular spaces: a cross-sectional study

Shuna Yang[1], Wei Qin[1], Lei Yang[1], Huimin Fan[1], Yue Li[1], Jiangmei Yin[1], Wenli Hu[1*]

1: Department of Neurology, Beijing Chaoyang Hospital, Capital Medical University, Beijing, China

*: Corresponding Author

Email: huwenli@sina.com, Telephone: +8601085231376, Fax: 011-86-10-65926388

Institution address: Beijing Chaoyang Hospital, No.8 South Gongti Road, Chaoyang District, Beijing, China

Abstract

Objectives: Recent studies reported that 24-hour ambulatory blood pressure variability (ABPV) was associated with lacunar infarction and white matter hyperintensities (WMH). However, the relationship between ABPV and enlarged perivascular spaces (EPVS) hasn't been investigated. Thus, our study aimed to investigate whether ABPV is associated with EPVS by 24-hour ambulatory blood pressure monitoring (ABPM).

Design: We conducted this study as a cross-sectional study.

Settings: The study was based on patients who presented for physical examinations in our hospital from May 2013 to Jun 2016.

Participants: Patients with both brain MRI scans and 24-hour ABPM were included and patients with acute stroke, a history of severe stroke and some other severe diseases were excluded. A total of 573 Chinese patients were prospectively enrolled in this study.

Primary and secondary outcome measures: EPVS in basal ganglia (BG) and white matter (WM) were identified on MRI and classified into three categories by the severity. WMH were scored by Fazekas scale. Coefficient of variation (CV) and standard deviation (SD) were considered as metrics of ABPV. Spearman correlation analysis and ordinal logistic regression analysis were used to assess the relationship between ABPV and EPVS.

Results: There were statistical differences among the subgroups stratified by the severity of EPVS in BG in the following ABPV metrics: SD and CV of systolic blood pressure (SBP), CV of diastolic blood pressure (DBP) in 24-hour, daytime and nighttime and SD of DBP in nighttime. The above ABPV metrics were positively associated with the degree of EPVS. The association was unchanged after adjusting for confounders. Spearman correlation analysis showed ABPV wasn't related to the degree of EPVS in WM.

Conclusion: ABPV was independently associated with EPVS in BG after controlling for the blood pressure, but not in WM. Pathogenesis of EPVS in BG and WM might be different.

Keywords cerebral small vessel disease, enlarged perivascular spaces, Virchow-Robin spaces, blood pressure variability, ambulatory blood pressure monitoring

Strengths and limitations of this study

- Assessments of EPVS and WMH were performed by two experienced neurologists blinded to clinical information and disagreements were resolved by consensus, which ensure the accuracy of the assessments.
- Detailed information on some confounders crucial to the interpretation of EPVS was collected and ordinal logistic regression analysis was performed to determine the independency of association.
- The study was based on a population who presented to the hospital for physical exam in a single center and the cohort may not represent the general population.
- This was a cross-sectional study, and the causal relationship between ABPV and EPVS could not be established.

INTRODUCTION

Perivascular spaces, or Virchow-Robin spaces, are perivascular compartments surrounding the small penetrating cerebral vessels, serving as an important drainage system for interstitial fluids and solute in the brain[1]. They can dilate with accumulation of the interstitial fluids[2, 3]. Enlarged perivascular spaces (EPVS) appear as punctate or linear signal intensities similar to cerebrospinal fluids (CSF) on all MRI sequences in white matter (WM), basal ganglia (BG), hippocampus and brainstem[4, 5]. Recent studies indicated that EPVS were a magnetic resonance imaging (MRI) marker of cerebral small vessel diseases (CSVD) and were associated with other morphological features of CSVD such as white matter hyperintensities (WMH) and lacunes[6, 7]. Some studies found EPVS were associated with impaired cognitive function[5], incident dementia[8] and sleep disorders[9]. Therefore, it is of clinical importance to understand the risk factors for EPVS and search for treatable options in the future.

24-hour ambulatory blood pressure monitoring (ABPM) is proven to be a more useful and scientific method to predict blood pressure-related brain damage than single

office blood pressure measurement[10, 11]. Ambulatory blood pressure variability (ABPV) could be well documented by 24-hour ABPM. Previous studies demonstrated higher ABPV increased the risk of cardiovascular events[12, 13], WMH, lacunar infarction, and cognitive decline[14, 15]. WMH, lacunar infarction and EPVS are all neuroimaging features of CSVD and share some risk factors, such as age and hypertension[16]. However, the relationship between ABPV and EPVS has never been investigated. Thus in the present study, we aimed to investigate whether ABPV, which was reflected by 24-hour ABPM, was independently associated with EPVS.

METHODS

Study subjects

We conducted this study as a cross-sectional study. The patients who presented for physical examination to Medicine Department or Neurology Department of Beijing Chaoyang Hospital Affiliated to Capital Medical University were prospectively identified from May 2013 to Jun 2016. They were screened according to our inclusion and exclusion criteria. The number of arriving patients during the study period, inclusion and exclusion criteria determined the sample size. Inclusion criteria were: (1) patients underwent both brain MRI scans and 24-hour ABPM within 1 month; (2) patients agreed to participate in our study and signed an informed consent. The following patients were excluded: (1) patients with acute stroke, Parkinson disease, dementia, severe traumatic or toxic or infectious brain injury, and brain tumor; (2) patients with severe heart disease, recent myocardial infarction or angina pectoris disorders, severe infections, severe nephrosis or liver disease, thrombotic diseases and tumor; (3) patients with history of severe ischemic (the largest diameter of infarct size ＞20mm on diffusion-weighted imaging and fluid attenuated inversion recovery) or hemorrhagic stroke because of difficulty assessments on EPVS; (4) patients with invalid 24-hour ABPM data (The 24-h ABPM data were considered invalid if measurement was < 70%, < 1 measurement per hour during daytime, and < 6 in total during nighttime).

Assessments of EPVS and WMH

The neurological image examinations were performed in Radiology Department of

our hospital. MR imagines were acquired on a 3.0 T MR scanner (Siemens, Erlangen, Germany).

EPVS were defined as CSF-like signal intensity lesions of round, ovoid, or linear shape of <3mm and located in areas supplied by perforating arteries[6, 17]. We distinguished lacune from EPVS by their larger size (>3mm), spheroid shape and surrounding hyperintensities on FLAIR. WMH were defined as hyperintense signals on T2-weighted and FLAIR and decreased signal intensities on T1-weighted MR imaging.

EPVS in BG and WM were separately assessed according to the scales which were used in other studies[18, 19]. In BG, EPVS were rated according to the number in the slice containing the maximum amount of EPVS. The grades of EPVS were rated as following: grade 1: < 5 EPVS, grade 2: 5 to 10 EPVS, grade 3: > 10 but still countable, and grade 4: infinite number of EPVS. In WM, EPVS were scored as follows: grade 1：<10 EPVS in total WM, grade 2：>10 in total WM and <10 in the slice containing the maximum number of EPVS, grade 3：10 to 20 EPVS in the slice containing the maximum number of EPVS, grade 4：> 20 in the slice containing the maximum number of EPVS. We classified EPVS into three categories: degree 1 = grade 1; degree 2 = grade 2; degree 3 = grade 3 or 4.

WMH were scored by Fazekas scale. The detailed description of assessments has been previously published[20]. Periventricular and deep WMH were evaluated separately and then added together as Fazekas scores.

The intrarater agreement for the rating of EPVS and WMH was assessed on a random sample of 100 individuals with a month interval between the first and second readings. Assessments of EPVS and WMH were performed by two experienced neurologists blinded to clinical information to avoid bias. Random scans of 100 individuals were independently examined by the two experienced neurologists blinded to each other's readings. The *k* statistics of intrarater and interrater agreement was 0.80 or above, indicating good reliability. Disagreement was resolved by discussing with other co-authors.

24-hour ambulatory blood pressure monitoring

24-hour ABPM was performed using an automated system (FB-250; Fukuda Denshi, Tokyo, Japan). BP was measured every 30 minutes during the daytime (8:00 AM to 11:00 PM) and every 60 minutes during the nighttime (11:00 PM to 8:00 AM). We excluded a 2-hour transition period around the reported rising and retiring times. The mean systolic blood pressure (SBP), diastolic blood pressure (DBP), coefficient of variation (CV) and standard deviation (SD) of SBP and DBP during 24-hour, daytime, and nighttime were collected. The CV value was defined as the ratio between the SD and the mean SBP or DBP at the same periods. SD and CV were considered as metrics of BPV in this study. Patients continued taking their previous medications, and we registered the use of anti-hypertension drugs.

Statistical analysis

Continuous variables were presented as mean values ± SD and compared with ANOVA for factors with a normal distribution, whereas no normally distributed variables were compared with Kruskal–Wallis test as appropriate. Categorical variables were expressed as percentages and compared using the chi-square test. Spearman correlation analysis was used to calculate the association between ABPV and the severity of EPVS. In addition, ordinal logistic regression analysis was performed to determine whether the ABPV was independently associated with EPVS after adjusting for other confounders. The results were based on valid data; missing data were excluded. Analyses were performed with Statistical Package for Social Sciences (SPSS version21.0), and statistical significance was accepted at the $p < 0.05$.

RESULTS

Baseline characteristics of the study participants

742 patients underwent both brain MRI scans and 24-hour ABPM within 1 month in the Medicine Department or Neurology Department of our hospital from May 2013 to Jun 2016. 40 patients were excluded because of acute stroke, 21 were excluded because of history of severe or hemorrhagic stroke, 15 were excluded because of a history of tumor and 93 were excluded because of invalid ABPM data, leaving 573 patients enrolled in the present study. None of them had missing data. There were no

statistical differences (P＞0.05) in age, body mass index, proportion of male, current smoking, current alcohol, diabetes, hypertension, coronary artery atherosclerosis disease and using of anti-hypertensive drugs between the excluded subjects and the final group (Supplementary file). Table 1 showed the characteristics of all enrolled subjects and subgroups stratified by the degree of EPVS in different brain regions. Age, Fazekas scale, proportion of hypertension and stroke/TIA, levels of blood urea nitrogen and creatinine increased with the degree of EPVS in BG increasing. There were statistical differences in age, Fazekas scale and proportion of coronary artery atherosclerosis disease (CAD) among subgroups based on the degree of EPVS in WM.

There were statistical differences in the mean SBP during 24-hour, daytime, and nighttime among the categories stratified by the degree of EPVS in BG. The results of spearman correlation analysis showed SBP was positively related to higher degree of EPVS in BG during all periods (SBP of 24-hour: r=0.23, p < 0.01; SBP of daytime: r=0.25, p < 0.01; SBP of nighttime: r=0.30, p < 0.01). The mean DBP of daytime and nighttime increased with the degree of EPVS in WMH increasing. However, the results of spearman correlation analysis showed that DBP levels were not associated with higher numbers of EPVS in CSO (p > 0.05).

Table 1. General characteristics of all enrolled subjects and subgroups stratified by the severity of EPVS

Characteristics	All patients	EPVS in BG			EPVS in WM		
		Degree 1	Degree 2	Degree 3	Degree 1	Degree 2	Degree 3
n (%)	573	244 (42.6%)	179 (31.2%)	150 (26.2%)	200 (34.9%)	207 (36.1%)	166 (29.0%)
Age, years	67.8±14.8	61.4±14.4**	67.6±13.8**	78.3±9.6**	70.45±15.2**	66.25±14.4**	66.46±14.3**
Sex, male (%)	355 (62.0)	143 (58.6)	108 (60.3)	104 (69.3)	115 (57.5)	128 (61.8)	112 (67.5)
Current smoking (%)	162 (28.3)	83 (34.0)*	61(34.1)*	18(12.0)*	52 (26.0)	60 (29.0)	50 (30.1)
Current alcohol (%)	126 (22.0)	62 (25.4)*	45 (25.1)*	19 (12.7)*	36 (18.0)	50 (24.2)	40 (24.1)
Hypertension (%)	420 (73.3)	170 (69.7)*	122 (68.2)*	128 (85.3)*	150 (75.0)	145 (70.5)	125 (74.7)
Diabetes (%)	191 (33.3)	78 (32.0)	59 (33.0)	54 (36.0)	71 (35.5)	62 (30.0)	58 (34.9)

CAD (%)	140 (24.4)	48 (19.7)	48 (26.8)	44 (29.3)	61 (30.5) *	45 (21.7) *	34 (20.5) *
Stroke or TIA (%)	125 (21.8)	40 (16.4)**	33 (18.4)**	52 (34.7)**	49 (24.5)	39 (18.8)	37 (22.2)
BMI, kg/m^2	25.6±3.5	25.6±3.4	25.3±3.5	25.8±3.5	25.8±3.4	25.4±3.5	25.5±3.5
HDL, mmol/L	1.2±0.4	1.2±0.4	1.2±0.4	1.2±0.3	1.2±0.4	1.2±0.4	1.2±0.3
LDL, mmol/L	2.5±0.8	2.5±0.8	2.5±0.8	2.3±08	2.4±0.8	2.4±0.8	2.5±0.7
HbA1, %	6.4±1.3	6.4±1.3	6.4±1.4	6.5±1.2	6.4±1.1	6.5±1.4	6.5±1.4
BUN, mmol/L	5.8±2.1	5.5±1.7**	5.9±2.6**	6.3±2.0**	6.0±2.5	5.7±1.9	5.8±1.9
Creatinine, umol/L	79.1±27.1	74.0±19.3**	81.7±32.6**	84.2±29.4**	81.2±27.4	77.7±27.3	78.3±26.4
Fazekas scale	3.1±1.8	2.2±1.4**	3.1±1.7**	4.7±1.5**	3.5±2.0**	2.9±1.7**	3.1±1.7**
Using of anti-hypertensive drugs (%)	342 (59.7)	130 (53.3) *	96 (53.6) *	116 (77.3) *	129 (64.5)	114 (55.1)	99 (59.6)
Class of anti-hypertensive drugs							
Dihydropyridinic CCB (%)	226 (39.4)	74 (30.3)	67 (37.4)	63 (42.0)	69 (34.5)	79 (38.2)	55 (33.1)
ACEI (%)	26 (4.5)	11 (4.5)	6 (3.4)	9 (6.0)	8 (4.0)	9 (4.3)	9 (5.7)
ARB (%)	160 (27.9)	70 (28.7)	46 (25.7)	44 (29.3)	69 (34.5) *	52 (25.1) *	39 (23.5) *
β-Blockers (%)	96 (16.8)	34 (13.9)	28 (15.6)	34 (22.7)	40 (20.0)	31 (15.0)	25 (15.1)
Nonloop diuretics (%)	39 (6.8)	20 (8.2)	12 (6.7)	7 (4.7)	16 (8.0)	13 (6.3)	10 (6.0)
24-hour							
SBP (mmHg)	133±16.4	129±15.6**	134±16.0**	138±16.5**	133±16.5	132±17.1	132.9±15.4
DBP (mmHg)	76±9.6	77±9.5	76±10.0	75±9.1	75±9.5*	76±9.6*	77±9.6*
Daytime							
SBP (mmHg)	135±16.6	130±16.0**	135±16.0**	141±16.4**	135±16.6	134±17.6	135±15.3
DBP (mmHg)	77±10.0	77±10.0*	77±10.3*	75±9.5*	75±9.9*	77±10.1*	78±9.9*
Nighttime							
SBP (mmHg)	129±19.8	123±18.5**	131±18.9**	137±19.9**	130±20.8	128±19.5	129±19.0
DBP (mmHg)	74±10.7	74±10.5	73±11.2	74±10.4	723±10.8	74±10.5	75±10.8

EPVS, enlarged perivascular spaces; BG, basal ganglia; WM, white matter; BMI, body mass index; CAD, coronary artery atherosclerosis disease; TIA, transient ischemic attack; HDL, high-density lipoprotein; LDL, low-density lipoprotein; HbA1c, hemoglobin A1c; BUN, blood urea nitrogen, CCB, calcium-channel blocker;

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker. * $p < 0.05$, * * $p < 0.01$.

Association between ABPV and EPVS in BG

SD and CV of ambulatory blood pressure in different categories stratified by the degree of EPVS in BG were presented in Table 2. There were statistical differences ($p < 0.05$) among the three subgroups stratified by the severity of EPVS in all of the following BPV metrics: SD and CV of SBP, CV of DBP during 24-hour, daytime and nighttime and SD of DBP during nighttime. Theses metrics gradually increased with the degree of EPVS increasing (Fig 1-3). The results of spearman correlation analysis demonstrated theses metrics were positively associated with the degree of EPVS in BG ($r>0$, $P<0.05$) (Table 3). The association between ABPV and EPVS were unchanged even after adjusting for demographic confounders (model 1), Fazekas scale (model 2) and the mean SBP or DBP during the same period (model 3), which indicated that the ABPV were independently associated with EPVS in BG. The results of ordinal logistic regression analysis were presented in Table 4.

Association between ABPV and EPVS in WM

SD and CV of ambulatory blood pressure in different categories stratified by degree of EPVS in WM were also presented in Table 2. There were statistical differences ($p < 0.05$) in SD of SBP, CV of SBP, SD of DBP and CV of DBP during 24-hour and daytime among the three categories. However, there were not linear trend among the three subgroups. The results of spearman correlation analysis showed there were no linear correlation between theses metrics and the degree of EPVS in WM (Table 3).

Table 2. Results of ABPV in all subjects and subgroups stratified by the severity of EPVS

	All patietns	EPVS in BG				EPVS in WM			
		Degree 1	Degree 2	Degree 3	P	Degree 1	Degree 2	Degree 3	P
24-hour									
SD of SBP, mmHg	18.28±5.27	16.93±4.76	18.57±4.56	20.13±6.21	＜0.001	18.86±5.56	17.36±5.11	18.73±4.99	0.004

SD of DBP, mmHg	12.56±3.58	12.22±3.56	12.62±3.34	13.05±3.86	0.149	12.83±3.76	11.85±3.32	13.14±3.56	0.001
CV of SBP, %	13.83±3.80	13.21±3.56	13.99±3.54	14.64±4.26	0.004	14.16±3.87	13.23±3.70	14.18±3.76	0.028
CV of DBP, %	16.68±4.74	16.03±4.68	16.82±4.46	17.55±5.04	0.013	17.22±4.76	15.78±4.72	17.14±4.60	0.001
Daytime									
SD of SBP, mmHg	18.02±5.70	16.66±4.93	18.21±5.35	19.99±6.65	＜0.001	18.68±5.98	16.99±5.47	18.50±5.49	0.004
SD of DBP, mmHg	12.56±4.01	12.25±3.80	12.51±3.93	13.12±4.40	0.241	12.81±4.06	11.76±3.71	13.26±4.17	0.001
CV of SBP, %	13.45±4.08	12.84±3.75	13.62±4.14	14.26±4.38	0.005	13.86±4.16	12.76±3.88	13.81±4.12	0.016
CV of DBP, %	16.48±5.19	15.84±4.77	16.47±5.24	17.54±5.63	0.024	16.98±4.88	15.47±5.12	17.15±5.48	0.002
Nighttime									
SD of SBP, mmHg	15.21±7.37	13.79±7.71	15.18±5.74	17.54±7.97	＜0.001	15.08±6.09	14.94±8.66	15.69±7.05	0.180
SD of DBP, mmHg	10.43±4.50	9.81±4.33	10.77±4.55	11.03±4.61	0.010	10.23±4.11	10.26±4.58	10.88±4.84	0.247
CV of SBP, %	11.85±5.37	11.22±5.53	11.77±4.56	12.95±5.84	0.005	11.69±4.62	11.70±5.95	12.23±5.48	0.411
CV of DBP, %	14.26±6.02	13.42±5.88	14.75±5.89	15.03±628	0.003	14.20±5.61	14.08±6.30	14.54±6.17	0.426

1 SBP: systolic blood pressure; DBP: diastolic blood pressure; CV: coefficient of
2 variation; SD: standard deviation.

3 **Table 3.** Results of spearman correlation analysis between the degree of EPVS and
4 ABPV

	EPVS in BG		EPVS in WM	
	r	P value	r	P value
24h				
SD of SBP	0.216	0.000	-0.013	0.762
SD of DBP	0.082	0.051	0.030	0.481
CV of SBP	0.137	0.001	-0.008	0.854
CV of DBP	0.123	0.003	-0.028	0.505
Daytime				

SD of SBP	0.205	0.000	-0.024	0.562
SD of DBP	0.065	0.120	0.031	0.459
CV of SBP	0.135	0.001	-0.023	0.585
CV of DBP	0.109	0.009	-0.017	0.679
Nighttime				
SD of SBP	0.229	0.000	0.020	0.637
SD of DBP	0.125	0.003	0.043	0.309
CV of SBP	0.136	0.001	0.027	0.521
CV of DBP	0.135	0.001	0.007	0.870

SBP: systolic blood pressure; DBP: diastolic blood pressure; CV: coefficient of variation; SD: standard deviation.

Table 4. Results of ordinal logistic regression analysis between ABPV and EPVS in BG

	Model 1		Model 2		Model 3	
	Odds ratio (95% CI)	P	Odds ratio (95% CI)	P	Odds ratio (95% CI)	P
24h						
SD of SBP	1.55 (1.32-1.83)	＜0.001	1.48 (1.25-1.75)	＜0.001	1.41 (1.19-1.68)	＜0.001
CV of SBP	1.47 (1.19-1.83)	＜0.001	1.48 (1.18-1.85)	0.001	1.60 (1.27-2.02)	＜0.001
CV of DBP	1.59 (1.13-2.24)	0.008	1.69 (1.18-2.42)	0.004	1.81 (1.25-2.60)	0.001
Daytime						
SD of SBP	1.44 (1.25-1.67)	＜0.001	1.39 (1.19-1.61)	＜0.001	1.31 (1.12-1.54)	0.001
CV of SBP	1.32 (1.08-1.61)	0.006	1.32 (1.08-1.62)	0.008	1.43 (1.16-1.77)	0.001
CV of DBP	1.49 (1.10-2.04)	0.011	1.59 (1.15-2.19)	0.005	1.67 (1.21-2.31)	0.002
Nighttime						
SD of SBP	1.29 (1.15-1.46)	＜0.001	1.25 (1.11-1.40)	＜0.001	1.21 (1.07-1.37)	0.002
SD of DBP	1.39 (1.15-1.67)	＜0.001	1.33 (1.11-1.61)	0.003	1.31 (1.12-1.54)	0.001
CV of SBP	1.27 (1.09-1.48)	0.002	1.26 (1.08-1.47)	0.003	1.31 (1.08-1.58)	0.006
CV of DBP	1.19 (1.04-1.36)	0.013	1.20 (1.04-1.37)	0.012	1.21 (1.05-1.39)	0.008

Results of ordinal regression analysis presented as OR per 5% increase in CV of

blood pressure and 5 mmHg in SD of blood pressure.

Model1: adjusted for age, smoking, alcohol, hypertension, stroke/TIA, BUN, creatinine and using of anti-hypertensive drugs.

Model2: model 1 + Fazekas scale.

Model3: model 2 + the mean SBP or DBP during the same period.

DISCUSSION

In this study, we explored the relationship between ABPV and EPVS based on the population who presented for physical exam. Our data suggested that all of the following metrics: SD of SBP, CV of SBP and CV of DBP during 24-hour, daytime and nighttime and SD of DBP during nighttime were positively associated with the degree of EPVS in BG. The association between the above ABPV metrics and EPVS in BG were unchanged after adjusting for demographic confounders, Fazekas scale and the mean SBP or DBP during the same period. Although there were statistical differences in ABPV metrics during 24-hour and daytime among the three subgroups stratified by EPVS severity in WM, there were no linear correlation between ABPV and the degree of EPVS in WM. In addition, we found age, Fazekas scale, hypertension, stroke/transient ischemic attack (TIA), levels of blood urea nitrogen and creatinine were positively associated with the degree of EPVS in BG.

There were methodological strengths of our study. We recruited participants strictly according to inclusion and exclusion criteria to avoid selection bias. The patients with acute cerebrovascular and cardiovascular disorders were excluded to avoid the impact of the acute stroke, recent myocardial infarction or angina pectoris on blood pressure. The patients with a history of severe ischemic (the largest diameter of infarct size＞20mm on diffusion-weighted imaging and fluid attenuated inversion recovery) or hemorrhagic stroke were excluded because of difficulty and inaccurate assessment on EPVS. In addition, the assessments of EPVS and WMH were performed by two experienced neurologists blinded to clinical information and disagreements were resolved by consensus, which ensure the accuracy of the assessments. We collected detailed information on vascular confounders, WMH, levels of blood urea nitrogen and creatinine, which are crucial to the interpretation of EPVS[6, 21]. So we think the

reliability of the data is high. There were some limitations in our study. First, our study was based on a population who visited the hospital for physical exam in a single center and the cohort may not represent the general population. According to our observation, these people had a higher economic status than that of the general population in China, and some of them showed more symptoms of anxiety. But it's regrettable that we didn't assess the anxiety symptoms by the Hamilton Anxiety Rating Scale or assess the patients' education level. Second, this was a cross-sectional study, and the causal relationship between ABPV and EPVS could not be established. Third, all participants underwent 24-hour ABPM which could only show short-term ABPV. It has been demonstrated that the prognostic significance of BPV on vascular diseases is weaker for short-term than for long-term BPV[22].

This is the first study to investigate the relationship between ABPV and EPVS. Previously, several studies investigated the relationship between EPVS and hypertension. In a prospective, multicenter, hospital-based study, Zhang CQ et al[19] found hypertension was associated with the severity of EPVS in WM, not in BG. Klarenbeek P et al[23] investigated the association between ABP levels and EPVS in first-ever lacunar stroke patients. They found higher day systolic, day diastolic and 24-hour diastolic BP levels were independently associated EPVS in BG, and no relation between ABP levels and EPVS in WM. We also analyzed the correlation between ABP levels and EPVS. We found ABP levels were associated with EPVS in BG, but not in WMH, which is consistent with Klarenbeek P et al.'s study. However, we found only SBP was positively related to higher degree of EPVS in BG in all periods, and no relation between DBP and EPVS, which are different form previous results. The different study population and different scoring methods of assessing EPVS may partly lead to the different results. Our data suggested that SD of SBP, CV of SBP and CV of DBP in all periods were positively associated with the degree of EPVS in BG, but not in WM. The present study couldn't explain the phenomenon. This may be caused by different pathogenesis of EPVS at the different locations[18, 19, 24]. Previous studies have found the anatomical structure of EPVS located in BG and WM were different[25]. The arteries in the basal ganglia are surrounded by 2 distinct

coats of leptomeninges separated by a perivascular space which is continuous with the perivascular space around arteries in the subarachnoid space. Whereas there are only single periarterial layer of leptomeninges surrounding the arteries in the cerebral cortex and they penetrate into the white matter. Drainage of interstitial fluid from the brain to cervical lymph nodes may mainly go along perivascular spaces in WM rather than in BG[3, 26]. In addition, the impact of age, hypertension on EPVS seems to be stronger for EPVS located in BG than for those located in WM[18]. Similarly, the association between EPVS and the load of WMH, taken as a marker of CSVD, also appears to be stronger in BG than in WM. Thus, their dilations may present differences in terms of risk factors as well as in mechanisms in BG and WM. However, the reason SBP is related differently in these two locations remains unclear because there are a very limited number of studies on mechanisms underlying dilation of perivascular spaces in BG and WM. Several studies have demonstrated higher ABPV increased the risk of neuroimaging features of CSVD, such as WMH and lacunar infarction[14, 15]. Our results found higher ABPV was independently associated with higher degree of EPVS in BG, which support the finding that EPVS in BG are a separate marker of CSVD.

An increased permeability of the small vessel walls and blood brain barrier (BBB) are considered to contribute to the development of EPVS, which has been reported to be associated with damage of microvascular endothelial cells and their tight junctions[1, 16, 27]. Higher ABPV would lead to more mechanical stress on the wall vessel, endothelial injury[28] and arterial stiffness[29]. Therefore, it is reasonable that high ABPV contribute to the development of EPVS by damaging endothelial cells. Our results may remind clinicians that they should pay attention to patients' ABPV and lower patients' ABPV in their clinical practices. In the future, a prospective cohort study will help better establish the relationship between ABPV and EPVS.

CONCLUSION

SD of SBP, CV of SBP and CV of DBP during all periods and SD of DBP during nighttime were positively associated with the degree of EPVS in BG. The association was unchanged after adjusting for confounders. No relation was found between ABPV

and EPVS in WM. It is important for clinicians to reduce both patients' high blood pressure levels and ABPV.

Contributors WH conceived and designed the experiments. SY, WQ, LY and HF participated in the data collection. JY and YL participated in the analysis of the data. SY drafted the manuscript. WH has given final approval of the version to be published. All authors read and approved the final manuscript.

Funding This work is supported by National Natural Science Foundation of China (Grant No. 81271309).

Conflict of Interest None declared.

Ethic approval The study was approved by the Ethics Committee of Beijing Chaoyang Hospital Affiliated to Capital Medical University and was performed in accordance with the declaration of Helsinki.

Acknowledgements

The authors thank all the study participants.

Data sharing statement No additional data are available.

Reference

1. Kwee RM, Kwee TC. Virchow-robin spaces at mr imaging. *Radiographics : a review publication of the Radiological Society of North America, Inc*. 2007;27:1071-1086
2. Ozturk MH, Aydingoz U. Comparison of mr signal intensities of cerebral perivascular (virchow-robin) and subarachnoid spaces. *Journal of computer assisted tomography*. 2002;26:902-904
3. Abbott NJ. Evidence for bulk flow of brain interstitial fluid: Significance for physiology and pathology. *Neurochemistry international*. 2004;45:545-552
4. Zhu YC, Dufouil C, Mazoyer B, Soumare A, Ricolfi F, Tzourio C, Chabriat H. Frequency and location of dilated virchow-robin spaces in elderly people: A population-based 3d mr imaging study. *AJNR. American journal of neuroradiology*. 2011;32:709-713
5. Maclullich AM, Wardlaw JM, Ferguson KJ, Starr JM, Seckl JR, Deary IJ. Enlarged perivascular spaces are associated with cognitive function in healthy elderly men. *Journal of neurology, neurosurgery, and psychiatry*. 2004;75:1519-1523
6. Wardlaw JM, Smith EE, Biessels GJ, Cordonnier C, Fazekas F, Frayne R, Lindley RI, O'Brien JT, Barkhof F, Benavente OR, Black SE, Brayne C, Breteler M, Chabriat H, Decarli C, de Leeuw FE, Doubal F, Duering M, Fox NC, Greenberg S, Hachinski V, Kilimann I, Mok V, Oostenbrugge R, Pantoni L, Speck O, Stephan BC, Teipel S, Viswanathan A, Werring D, Chen C, Smith C, van Buchem M, Norrving B, Gorelick PB, Dichgans M. Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. *The Lancet. Neurology*. 2013;12:822-838

7. Doubal FN, MacLullich AM, Ferguson KJ, Dennis MS, Wardlaw JM. Enlarged perivascular spaces on mri are a feature of cerebral small vessel disease. *Stroke*. 2010;41:450-454
8. Zhu YC, Dufouil C, Soumare A, Mazoyer B, Chabriat H, Tzourio C. High degree of dilated virchow-robin spaces on mri is associated with increased risk of dementia. *Journal of Alzheimer's disease : JAD*. 2010;22:663-672
9. Berezuk C, Ramirez J, Gao F, Scott CJ, Huroy M, Swartz RH, Murray BJ, Black SE, Boulos MI. Virchow-robin spaces: Correlations with polysomnography-derived sleep parameters. *Sleep*. 2015;38:853-858
10. Ohkubo T, Hozawa A, Nagai K, Kikuya M, Tsuji I, Ito S, Satoh H, Hisamichi S, Imai Y. Prediction of stroke by ambulatory blood pressure monitoring versus screening blood pressure measurements in a general population: The ohasama study. *Journal of hypertension*. 2000;18:847-854
11. Shimada K, Kawamoto A, Matsubayashi K, Ozawa T. Silent cerebrovascular disease in the elderly. Correlation with ambulatory pressure. *Hypertension (Dallas, Tex. : 1979)*. 1990;16:692-699
12. Conen D, Bamberg F. Noninvasive 24-h ambulatory blood pressure and cardiovascular disease: A systematic review and meta-analysis. *Journal of hypertension*. 2008;26:1290-1299
13. Rothwell PM. Does blood pressure variability modulate cardiovascular risk? *Current hypertension reports*. 2011;13:177-186
14. Yamaguchi Y, Wada M, Sato H, Nagasawa H, Koyama S, Takahashi Y, Kawanami T, Kato T. Impact of ambulatory blood pressure variability on cerebral small vessel disease progression and cognitive decline in community-based elderly japanese. *American journal of hypertension*. 2014;27:1257-1267
15. Filomena J, Riba-Llena I, Vinyoles E, Tovar JL, Mundet X, Castane X, Vilar A, Lopez-Rueda A, Jimenez-Balado J, Cartanya A, Montaner J, Delgado P. Short-term blood pressure variability relates to the presence of subclinical brain small vessel disease in primary hypertension. *Hypertension (Dallas, Tex. : 1979)*. 2015;66:634-640; discussion 445
16. Wardlaw JM, Smith C, Dichgans M. Mechanisms of sporadic cerebral small vessel disease: Insights from neuroimaging. *The Lancet. Neurology*. 2013;12:483-497
17. Groeschel S, Chong WK, Surtees R, Hanefeld F. Virchow-robin spaces on magnetic resonance images: Normative data, their dilatation, and a review of the literature. *Neuroradiology*. 2006;48:745-754
18. Zhu YC, Tzourio C, Soumare A, Mazoyer B, Dufouil C, Chabriat H. Severity of dilated virchow-robin spaces is associated with age, blood pressure, and mri markers of small vessel disease: A population-based study. *Stroke*. 2010;41:2483-2490
19. Zhang C, Chen Q, Wang Y, Zhao X, Wang C, Liu L, Pu Y, Zou X, Du W, Pan Y, Li Z, Jing J, Wang D, Luo Y, Wong KS. Risk factors of dilated virchow-robin spaces are different in various brain regions. *PloS one*. 2014;9:e105505
20. Fazekas F, Chawluk JB, Alavi A, Hurtig HI, Zimmerman RA. Mr signal abnormalities at 1.5 t in alzheimer's dementia and normal aging. *AJR. American journal of roentgenology*. 1987;149:351-356
21. Yamamoto Y, Ohara T, Nagakane Y, Tanaka E, Morii F, Koizumi T, Akiguchi I. Chronic kidney disease, 24-h blood pressure and small vessel diseases are independently associated with cognitive impairment in lacunar infarct patients. *Hypertension research : official journal*

of the Japanese Society of Hypertension. 2011;34:1276-1282

22. Rothwell PM, Howard SC, Dolan E, O'Brien E, Dobson JE, Dahlof B, Sever PS, Poulter NR. Prognostic significance of visit-to-visit variability, maximum systolic blood pressure, and episodic hypertension. *Lancet (London, England)*. 2010;375:895-905
23. Klarenbeek P, van Oostenbrugge RJ, Lodder J, Rouhl RP, Knottnerus IL, Staals J. Higher ambulatory blood pressure relates to enlarged virchow-robin spaces in first-ever lacunar stroke patients. *Journal of neurology*. 2013;260:115-121
24. Satizabal CL, Zhu YC, Dufouil C, Tzourio C. Inflammatory proteins and the severity of dilated virchow-robin spaces in the elderly. *Journal of Alzheimer's disease : JAD*. 2013;33:323-328
25. Pollock H, Hutchings M, Weller RO, Zhang ET. Perivascular spaces in the basal ganglia of the human brain: Their relationship to lacunes. *Journal of anatomy*. 1997;191 (Pt 3):337-346
26. Weller RO, Subash M, Preston SD, Mazanti I, Carare RO. Perivascular drainage of amyloid-beta peptides from the brain and its failure in cerebral amyloid angiopathy and alzheimer's disease. *Brain pathology (Zurich, Switzerland)*. 2008;18:253-266
27. Wuerfel J, Haertle M, Waiczies H, Tysiak E, Bechmann I, Wernecke KD, Zipp F, Paul F. Perivascular spaces--mri marker of inflammatory activity in the brain? *Brain : a journal of neurology*. 2008;131:2332-2340
28. Diaz KM, Veerabhadrappa P, Kashem MA, Thakkar SR, Feairheller DL, Sturgeon KM, Ling C, Williamson ST, Kretzschmar J, Lee H, Grimm H, Babbitt DM, Vin C, Fan X, Crabbe DL, Brown MD. Visit-to-visit and 24-h blood pressure variability: Association with endothelial and smooth muscle function in african americans. *Journal of human hypertension*. 2013;27:671-677
29. Schillaci G, Bilo G, Pucci G, Laurent S, Macquin-Mavier I, Boutouyrie P, Battista F, Settimi L, Desamericq G, Dolbeau G, Faini A, Salvi P, Mannarino E, Parati G. Relationship between short-term blood pressure variability and large-artery stiffness in human hypertension: Findings from 2 large databases. *Hypertension (Dallas, Tex. : 1979)*. 2012;60:369-377

Figure 1. The ABPV metrics of subgroups stratified by EPVS severity in BG during 24-hour. (a) CV of systolic blood pressure. (b) CV of diastolic blood pressure. (c) SD of systolic blood pressure. (d) SD of diastolic blood pressure.

Figure 2. The ABPV metrics of subgroups stratified by EPVS severity in BG during daytime. (a) CV of systolic blood pressure. (b) CV of diastolic blood pressure. (c) SD of systolic blood pressure. (d) SD of diastolic blood pressure.

Figure 3. The ABPV metrics of subgroups stratified by EPVS severity in BG during nighttime. (a) CV of systolic blood pressure. (b) CV of diastolic blood pressure. (c) SD of systolic blood pressure. (d) SD of diastolic blood pressure.

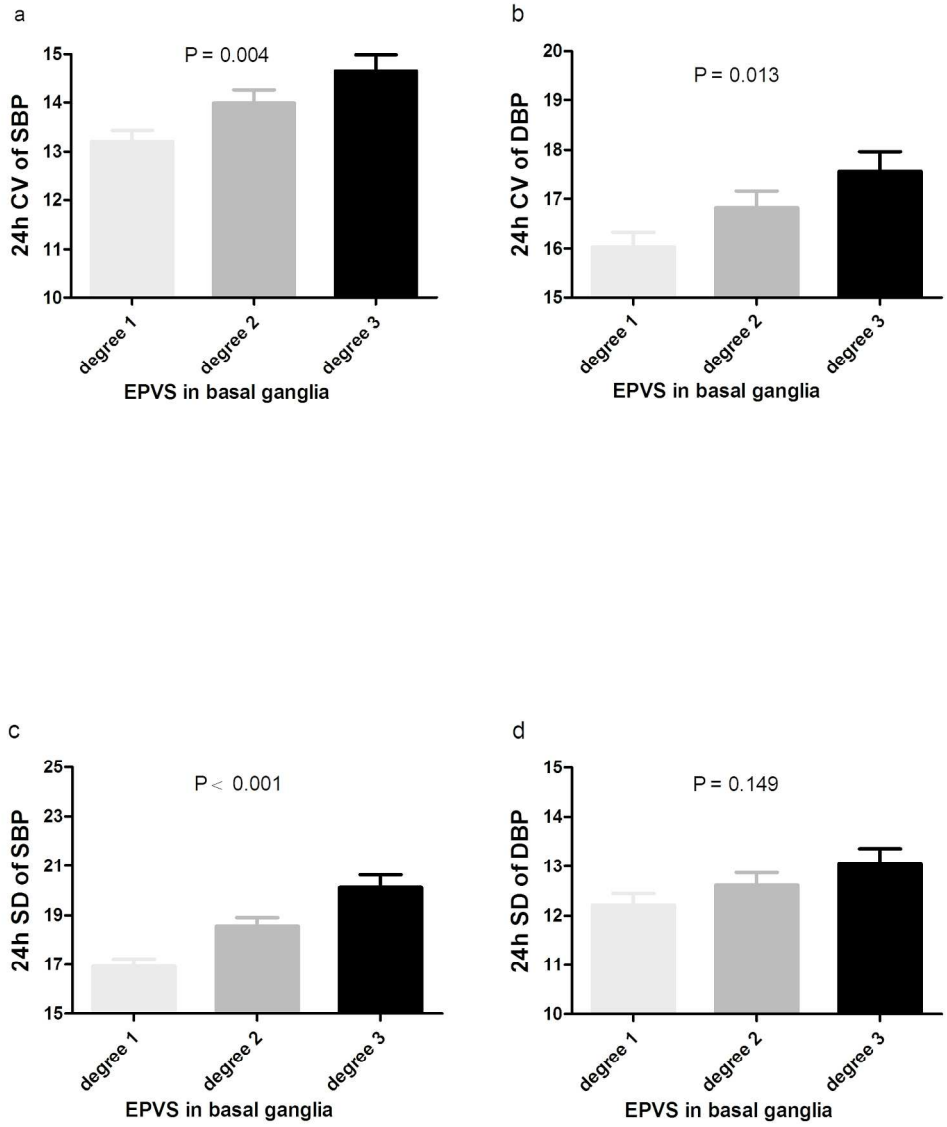


Figure 1. The ABPV metrics of subgroups stratified by EPVS severity in BG during 24-hour. (a) CV of systolic blood pressure. (b) CV of diastolic blood pressure. (c) SD of systolic blood pressure. (d) SD of diastolic blood pressure.

191x228mm (300 x 300 DPI)

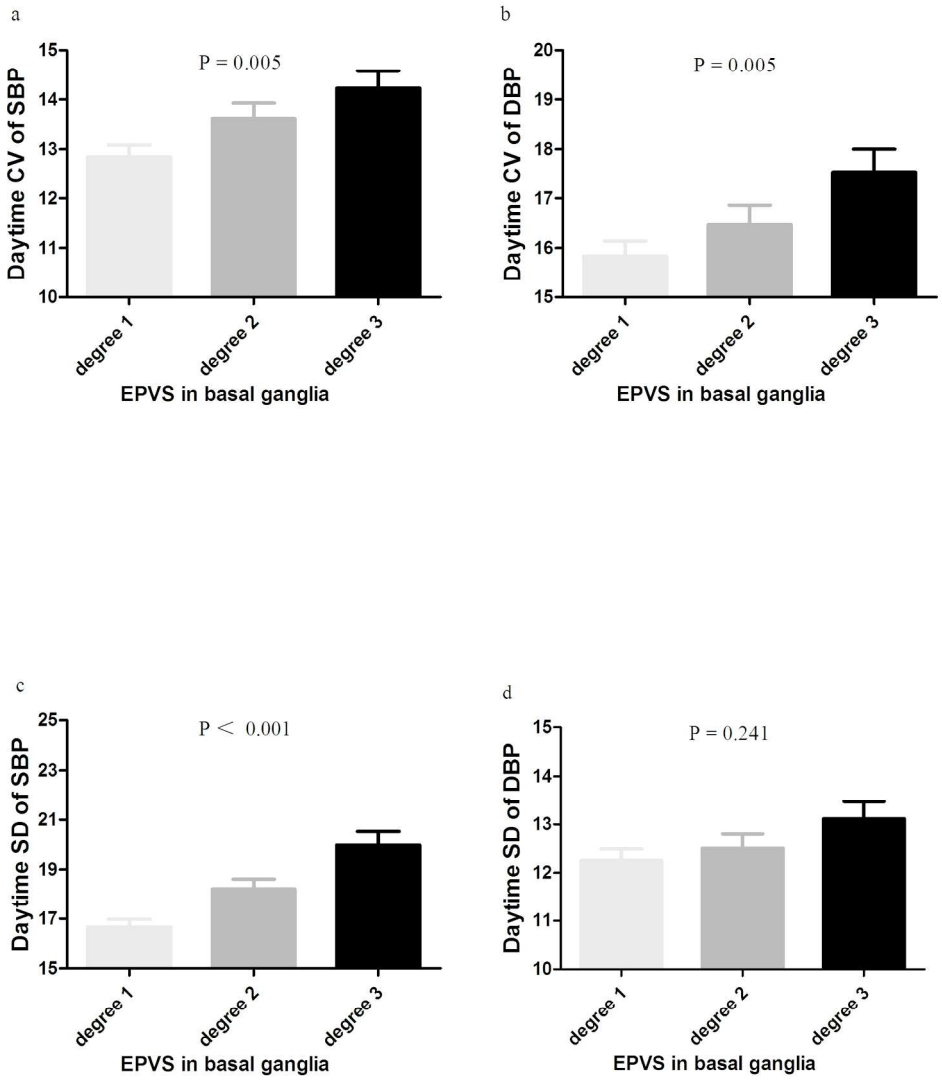


Figure 2. The ABPV metrics of subgroups stratified by EPVS severity in BG during daytime. (a) CV of systolic blood pressure. (b) CV of diastolic blood pressure. (c) SD of systolic blood pressure. (d) SD of diastolic blood pressure.

190x218mm (300 x 300 DPI)

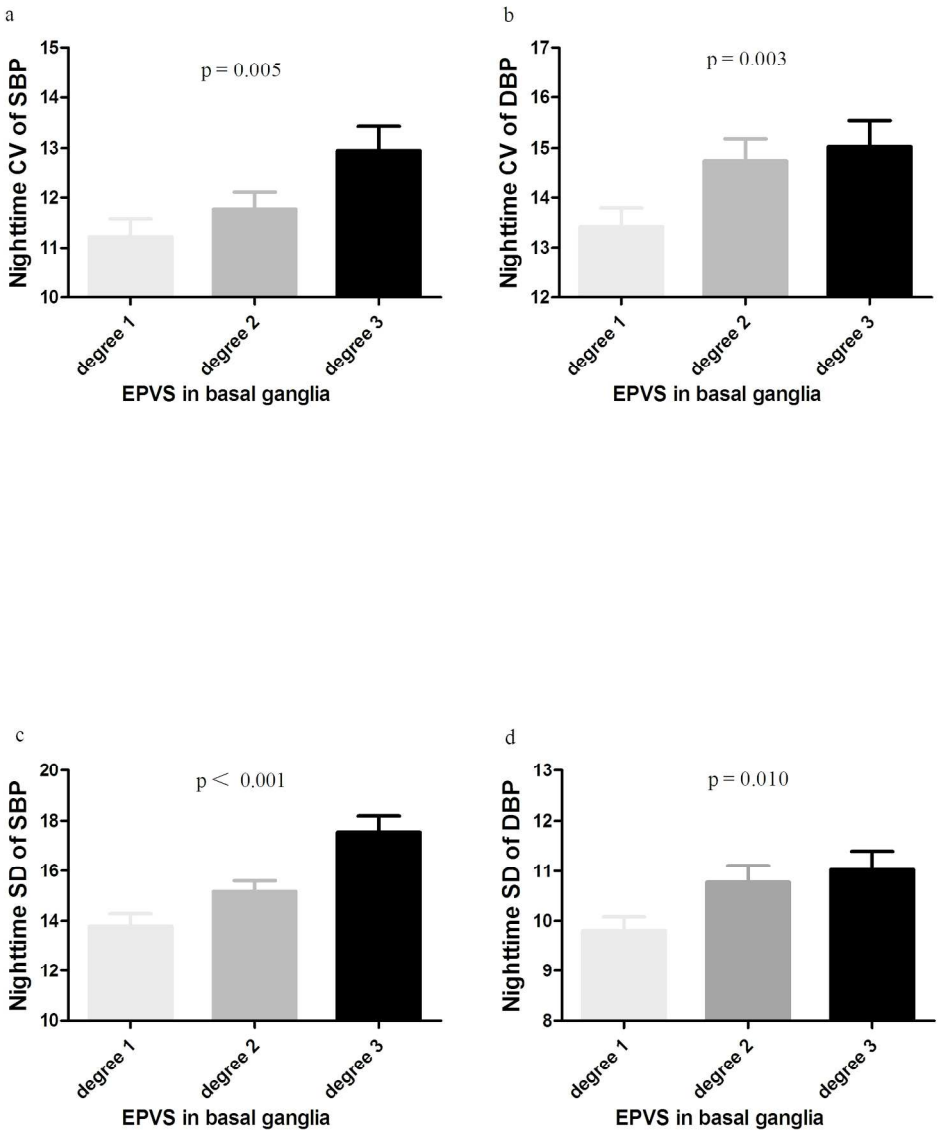
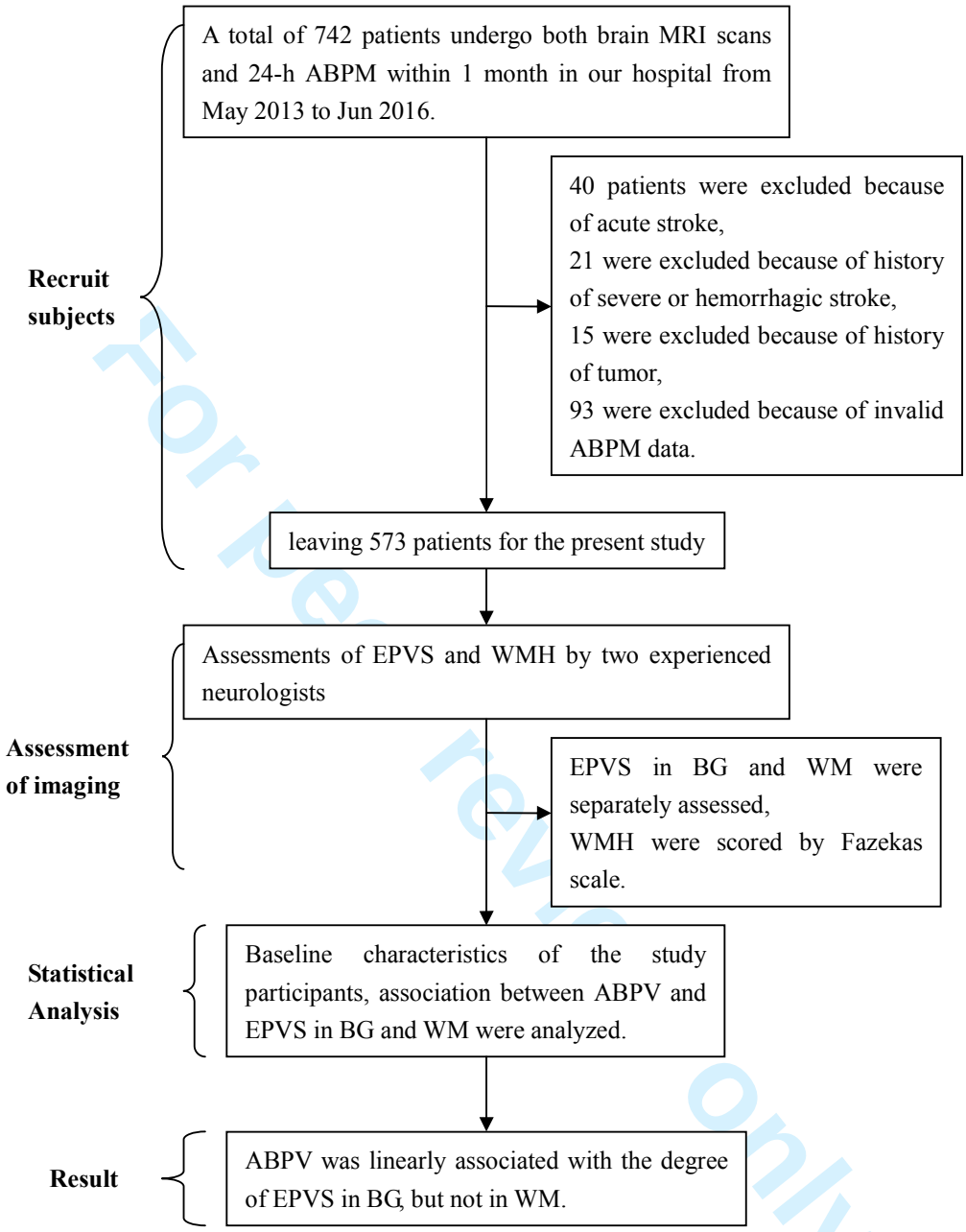


Figure 3. The ABPV metrics of subgroups stratified by EPVS severity in BG during nighttime. (a) CV of systolic blood pressure. (b) CV of diastolic blood pressure. (c) SD of systolic blood pressure. (d) SD of diastolic blood pressure.

189x227mm (300 x 300 DPI)

The comparison of general clinical characteristics between the included and excluded participants

Characteristics	enrolled patients	excluded patients	P
n	573	169	-
Age, years	67.8±14.8	69.6±9.6	0.443
Sex, male (%)	355 (62.0)	101(59.8)	0.607
Current smoking (%)	162 (28.3)	55(32.5)	0.283
Current alcohol (%)	126 (22.0)	42(24.9)	0.435
Hypertension (%)	420 (73.3)	115(68.0)	0.181
Diabetes (%)	191 (33.3)	44(26.0)	0.073
coronary atherosclerosis disease (%)	140 (24.4)	35(20.7)	0.316
body mass index, kg/m^2	25.6±3.5	25.1±3.0	0.160
Using of anti-hypertensive drugs (%)	342 (59.7)	99(58.6)	0.797



ABPM, ambulatory blood pressure monitoring; EPVS, enlarged perivascular spaces; WMH, white matter hyperintensities; BG, basal ganglia; WM, white matter.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	P1 and 2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	P2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	P3-4
Objectives	3	State specific objectives, including any prespecified hypotheses	P4
Methods			
Study design	4	Present key elements of study design early in the paper	P4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	P4
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	P4
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	P5-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	P5-6
Bias	9	Describe any efforts to address potential sources of bias	P4 and 5

Study size	10	Explain how the study size was arrived at	P4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	P6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	P6
		(*b*) Describe any methods used to examine subgroups and interactions	P6
		(*c*) Explain how missing data were addressed	P6
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	P6
		(b) Give reasons for non-participation at each stage	P6
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	P7
		(b) Indicate number of participants with missing data for each variable of interest	P7
Outcome data	15*	Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	P6-12
		(*b*) Report category boundaries when continuous variables were categorized	

		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	P12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	P12-13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	P13-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	P14-15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	P15

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

The relationship between ambulatory blood pressure variability and enlarged perivascular spaces: a cross-sectional study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2016-015719.R3
Article Type:	Research
Date Submitted by the Author:	29-Jun-2017
Complete List of Authors:	Yang, Shuna; Beijing Chaoyang Hospital, Neurology Qin, Wei; Beijing Chaoyang Hospital, Neurology Yang, Lei; Beijing Chaoyang Hospital, Neurology Fan, Huimin; Beijing Chaoyang Hospital, Neurology Li, Yue; Beijing Chaoyang Hospital, Neurology Yin, Jiangmei; Beijing Chaoyang Hospital, Neurology Hu, Wenli; Neurology
Primary Subject Heading:	Neurology
Secondary Subject Heading:	Health services research, Neurology
Keywords:	cerebral small vessel disease, enlarged perivascular spaces, Virchow-Robin spaces, blood pressure variability, ambulatory blood pressure monitoring

The relationship between ambulatory blood pressure variability and enlarged perivascular spaces: a cross-sectional study

Shuna Yang[1], Wei Qin[1], Lei Yang[1], Huimin Fan[1], Yue Li[1], Jiangmei Yin[1], Wenli Hu[1*]

1: Department of Neurology, Beijing Chaoyang Hospital, Capital Medical University, Beijing, China

*: Corresponding Author

Email: huwenli@sina.com, Telephone: +8601085231376, Fax: 011-86-10-65926388

Institution address: Beijing Chaoyang Hospital, No.8 South Gongti Road, Chaoyang District, Beijing, China

Abstract

Objectives: Recent studies reported that 24-hour ambulatory blood pressure variability (ABPV) was associated with lacunar infarction and white matter hyperintensities (WMH). However, the relationship between ABPV and enlarged perivascular spaces (EPVS) hasn't been investigated. Thus, our study aimed to investigate whether ABPV is associated with EPVS by 24-hour ambulatory blood pressure monitoring (ABPM).

Design: We conducted this study as a cross-sectional study.

Settings: The study was based on patients who presented for physical examinations in our hospital from May 2013 to Jun 2016.

Participants: Patients with both brain MRI scans and 24-hour ABPM were included and patients with acute stroke, a history of severe stroke and some other severe diseases were excluded. A total of 573 Chinese patients were prospectively enrolled in this study.

Primary and secondary outcome measures: EPVS in basal ganglia (BG) and white matter (WM) were identified on MRI and classified into three categories by the severity. WMH were scored by Fazekas scale. Coefficient of variation (CV) and standard deviation (SD) were considered as metrics of ABPV. Spearman correlation analysis and ordinal logistic regression analysis were used to assess the relationship between ABPV and EPVS.

Results: There were statistical differences among the subgroups stratified by the severity of EPVS in BG in the following ABPV metrics: SD and CV of systolic blood pressure (SBP), CV of diastolic blood pressure (DBP) in 24-hour, daytime and nighttime and SD of DBP in nighttime. The above ABPV metrics were positively associated with the degree of EPVS. The association was unchanged after adjusting for confounders. Spearman correlation analysis showed ABPV wasn't related to the degree of EPVS in WM.

Conclusion: ABPV was independently associated with EPVS in BG after controlling for blood pressure, but not in WM. Pathogenesis of EPVS in BG and WM might be different.

Keywords cerebral small vessel disease, enlarged perivascular spaces, Virchow-Robin spaces, blood pressure variability, ambulatory blood pressure monitoring

Strengths and limitations of this study

- Assessments of EPVS and WMH were performed by two experienced neurologists blinded to clinical information and disagreements were resolved by consensus, which ensure the accuracy of the assessments.
- Detailed information on some confounders crucial to the interpretation of EPVS was collected and ordinal logistic regression analysis was performed to determine the independency of association.
- The study was based on a population who presented to the hospital for physical exam in a single center and the cohort may not represent the general population.
- This was a cross-sectional study, and the causal relationship between ABPV and EPVS could not be established.

INTRODUCTION

Perivascular spaces, or Virchow-Robin spaces, are perivascular compartments surrounding the small penetrating cerebral vessels, serving as an important drainage system for interstitial fluids and solute in the brain[1]. They can dilate with accumulation of the interstitial fluids[2, 3]. Enlarged perivascular spaces (EPVS) appear as punctate or linear signal intensities similar to cerebrospinal fluids (CSF) on all MRI sequences in white matter (WM), basal ganglia (BG), hippocampus and brainstem[4, 5]. Recent studies indicated that EPVS were a magnetic resonance imaging (MRI) marker of cerebral small vessel diseases (CSVD) and were associated with other morphological features of CSVD such as white matter hyperintensities (WMH) and lacunes[6, 7]. Some studies found EPVS were associated with impaired cognitive function[5], incident dementia[8] and sleep disorders[9]. Therefore, it is of clinical importance to understand the risk factors for EPVS and search for treatable options in the future.

24-hour ambulatory blood pressure monitoring (ABPM) is proven to be a more useful and scientific method to predict blood pressure-related brain damage than single

office blood pressure measurement[10, 11]. Ambulatory blood pressure variability (ABPV) could be well documented by 24-hour ABPM. Previous studies demonstrated higher ABPV increased the risk of cardiovascular events[12, 13], WMH, lacunar infarction, and cognitive decline[14, 15]. WMH, lacunar infarction and EPVS are all neuroimaging features of CSVD and share some risk factors, such as age and hypertension[16]. However, the relationship between ABPV and EPVS has never been investigated. Thus in the present study, we aimed to investigate whether ABPV, which was reflected by 24-hour ABPM, was independently associated with EPVS.

METHODS

Study subjects

We conducted this study as a cross-sectional study. The inpatients for physical examinations in Medicine Department and Neurology Department of Beijing Chaoyang Hospital Affiliated to Capital Medical University were prospectively identified from May 2013 to Jun 2016. Some of them had a history of hypertension, diabetes mellitus, lacunar stroke or other risk factors for vascular diseases. They worried about the cerebrovascular diseases and wanted a well check up. They were screened according to our inclusion and exclusion criteria. The number of arriving patients during the study period, inclusion and exclusion criteria determined the sample size. Inclusion criteria were: (1) patients underwent both brain MRI scans and 24-hour ABPM within 1 month; (2) patients agreed to participate in our study and signed an informed consent. The following patients were excluded: (1) patients with acute stroke, Parkinson disease, dementia, severe traumatic or toxic or infectious brain injury, and brain tumor; (2) patients with severe heart disease, recent myocardial infarction or angina pectoris disorders, severe infections, severe nephrosis or liver disease, thrombotic diseases and tumor; (3) patients with history of severe ischemic (the largest diameter of infarct size＞20mm on diffusion-weighted imaging and fluid attenuated inversion recovery) or hemorrhagic stroke because of difficulty assessments on EPVS; (4) patients with invalid 24-hour ABPM data (The 24-h ABPM data were considered invalid if measurement times was < 70%, or < 1

measurement per hour during daytime, or < 6 in total during nighttime).

Assessments of EPVS and WMH

The neurological image examinations were performed in Radiology Department of our hospital. MR images were acquired on a 3.0 T MR scanner (Siemens, Erlangen, Germany).

EPVS were defined as CSF-like signal intensity lesions of round, ovoid, or linear shape of < 3mm and located in areas supplied by perforating arteries[6, 17]. We distinguished lacune from EPVS by their larger size (> 3mm), spheroid shape and surrounding hyperintensities on FLAIR. WMH were defined as hyperintense signals on T2-weighted and FLAIR and decreased signal intensities on T1-weighted MR imaging.

EPVS in BG and WM were separately assessed according to the scales which were used in other studies[18]. In BG, EPVS were rated according to the number in the slice containing the maximum amount of EPVS. The grades of EPVS were rated as following: grade 1: < 5 EPVS, grade 2: 5 to 10 EPVS, grade 3: 10 to 20 EPVS, and grade 4: > 20 EPVS. In WM, EPVS were scored as follows: grade 1：<10 EPVS in total WM, grade 2：>10 in total WM and <10 in the slice containing the maximum number of EPVS, grade 3：10 to 20 EPVS in the slice containing the maximum number of EPVS, grade 4：> 20 in the slice containing the maximum number of EPVS. We classified EPVS into three categories: degree 1 = grade 1; degree 2 = grade 2; degree 3 = grade 3 and 4.

WMH were scored by Fazekas scale. The detailed description of assessments has been previously published[19]. Periventricular and deep WMH were evaluated separately and then added together as Fazekas scores.

The intrarater agreement for the rating of EPVS and WMH was assessed on a random sample of 100 individuals with a month interval between the first and second readings. Assessments of EPVS and WMH were performed by two experienced neurologists blinded to clinical information to avoid bias. Random scans of 100 individuals were independently examined by the two experienced neurologists blinded to each other's readings. The *k* statistics of intrarater and interrater agreement was 0.80 or above,

indicating good reliability. Disagreement was resolved by discussing with other co-authors.

24-hour ambulatory blood pressure monitoring

24-hour ABPM was performed using an automated system (FB-250; Fukuda Denshi, Tokyo, Japan). BP was measured every 30 minutes during the daytime (8:00 AM to 11:00 PM) and every 60 minutes during the nighttime (11:00 PM to 8:00 AM). We excluded a 2-hour transition period around the reported rising and retiring times. The mean systolic blood pressure (SBP), diastolic blood pressure (DBP), coefficient of variation (CV) and standard deviation (SD) of SBP and DBP during 24-hour, daytime, and nighttime were collected. The CV value was defined as the ratio between the SD and the mean SBP or DBP at the same periods. SD and CV were considered as metrics of BPV in this study. Patients continued taking their previous medications, and we registered the use of anti-hypertension drugs.

Statistical analysis

Continuous variables were summarized as mean values ± standard deviation (SD) or median (interquartile range) according to whether its distribution conformed to a normal distribution. Analysis of variance (ANOVA) was used for comparison of continuous variables with both normal distribution and homogeneity of variance, whereas were compared with Kruskal–Wallis test as appropriate. Categorical variables were presented as absolute numbers and percentages. Chi-squared test was used for comparison of categorical variables. Spearman correlation analysis was used to calculate the association between ABPV and the severity of EPVS. The proportional odds assumption was met, thus ordinal logistic regression analysis was performed to determine whether the ABPV was independently associated with EPVS after adjusting for demographic confounders (model 1), Fazekas scale (model 2) and the mean SBP or DBP during the same period (model 3). The results were based on valid data; missing data were excluded. Analyses were performed with Statistical Package for Social Sciences (SPSS version21.0), and statistical significance was accepted at the $p < 0.05$.

RESULTS

Baseline characteristics of the study participants

742 patients underwent both brain MRI scans and 24-hour ABPM within 1 month in the Medicine Department or Neurology Department of our hospital from May 2013 to Jun 2016. 40 patients were excluded because of acute stroke, 21 were excluded because of history of severe or hemorrhagic stroke, 15 were excluded because of a history of tumor and 93 were excluded because of invalid ABPM data, leaving 573 patients enrolled in the present study. None of them had missing data. There were no statistical differences ($P>0.05$) in age, body mass index, proportion of male, current smoking, current alcohol, diabetes, hypertension, coronary artery atherosclerosis disease and using of anti-hypertensive drugs between the excluded subjects and the final group (Supplementary file). Table 1 showed the characteristics of all enrolled subjects and subgroups stratified by the degree of EPVS in different brain regions. Age, Fazekas scale, proportion of hypertension and stroke/TIA, levels of blood urea nitrogen and creatinine increased with the degree of EPVS in BG increasing. There were statistical differences in age, Fazekas scale and proportion of coronary artery atherosclerosis disease (CAD) among subgroups based on the degree of EPVS in WM.

There were statistical differences in the mean SBP during 24-hour, daytime, and nighttime among the categories stratified by the degree of EPVS in BG. The results of spearman correlation analysis showed SBP was positively related to higher degree of EPVS in BG during all periods (SBP of 24-hour: $r=0.23$, $p < 0.01$; SBP of daytime: $r=0.25$, $p < 0.01$; SBP of nighttime: $r=0.30$, $p < 0.01$). The mean DBP of daytime and nighttime increased with the degree of EPVS in WMH increasing. However, the results of spearman correlation analysis showed that DBP levels were not associated with higher numbers of EPVS in WM ($p > 0.05$).

Table 1. General characteristics of all enrolled subjects and subgroups stratified by the severity of EPVS

Characteristics	All patients	EPVS in BG			EPVS in WM		
		Degree 1	Degree 2	Degree 3	Degree 1	Degree 2	Degree 3

n (%)	573	244 (42.6%)	179 (31.2%)	150 (26.2%)	200 (34.9%)	207 (36.1%)	166 (29.0%)
Age, [a] years	69(55-81)	58(51-74)**	68(57-80)**	80(73-85)**	75(57-83)**	66(55-78)**	66(54-80)**
Sex, male (%)	355 (62.0)	143 (58.6)	108 (60.3)	104 (69.3)	115 (57.5)	128 (61.8)	112 (67.5)
Current smoking (%)	162 (28.3)	83 (34.0)*	61(34.1)*	18(12.0)*	52 (26.0)	60 (29.0)	50 (30.1)
Current alcohol (%)	126 (22.0)	62 (25.4)*	45 (25.1)*	19 (12.7)*	36 (18.0)	50 (24.2)	40 (24.1)
Hypertension (%)	420 (73.3)	170 (69.7)*	122 (68.2)*	128 (85.3)*	150 (75.0)	145 (70.5)	125 (74.7)
Diabetes (%)	191 (33.3)	78 (32.0)	59 (33.0)	54 (36.0)	71 (35.5)	62 (30.0)	58 (34.9)
CAD (%)	140 (24.4)	48 (19.7)	48 (26.8)	44 (29.3)	61 (30.5) *	45 (21.7) *	34 (20.5) *
Stroke or TIA (%)	125 (21.8)	40 (16.4)**	33 (18.4)**	52 (34.7)**	49 (24.5)	39 (18.8)	37 (22.2)
BMI, [b] kg/m^2	25.6±3.5	25.6±3.4	25.3±3.5	25.8±3.5	25.8±3.4	25.4±3.5	25.5±3.5
HDL, [a] mmol/L	1.16(1.00-1.38)	1.15(0.99-1.37)	1.17(0.98-1.41)	1.17(1.00-1.32)	1.17(1.00-1.38)	1.15(0.98-1.37)	1.15(0.99-1.34)
LDL, [a] mmol/L	2.40(1.90-2.94)	2.42(1.96-3.00)	2.47(1.88-2.93)	2.20(1.79-2.91)	2.32(1.88-2.94)	2.29(1.81-2.90)	2.51(2.00-3.00)
HbA1, [a] %	6.0(5.7-6.7)	6.0(5.7-6.7)	6.0(5.7-6.7)	6.1(5.7-6.7)	6.1(5.7-6.8)	6.0(5.7-6.6)	6.0(5.7-6.8)
BUN, [a] mmol/L	5.46(4.46-6.70)	5.18(4.34-6.34)**	5.36(4.32-6.59)**	5.97(4.82-7.42)**	5.50(4.55-7.02)	5.39(4.36-6.39)	5.42(4.50-6.81)
Creatinine, [a] umol/L	74.2(62.8-89.2)	70.2(59.7-84.6)**	74.5(63.7-89.6)**	81.9(66.4-94.1)**	77.0(62.8-92.1)	72.5(61.5-87.0)	74.0(62.9-89.1)
Fazekas scale [a]	3(2-5)	2(1-3)**	3(2-4)**	5(4-6)**	3(2-6)**	2(2-4)**	3(2-4)**
Using of anti-hypertensive drugs (%)	342 (59.7)	130 (53.3) *	96 (53.6) *	116 (77.3) *	129 (64.5)	114 (55.1)	99 (59.6)
Class of anti-hypertensive drugs							
Dihydropyridinic CCB (%)	226 (39.4)	74 (30.3)	67 (37.4)	63 (42.0)	69 (34.5)	79 (38.2)	55 (33.1)
ACEI (%)	26 (4.5)	11 (4.5)	6 (3.4)	9 (6.0)	8 (4.0)	9 (4.3)	9 (5.7)
ARB (%)	160 (27.9)	70 (28.7)	46 (25.7)	44 (29.3)	69 (34.5) *	52 (25.1) *	39 (23.5) *
β-Blockers (%)	96 (16.8)	34 (13.9)	28 (15.6)	34 (22.7)	40 (20.0)	31 (15.0)	25 (15.1)
Nonloop diuretics (%)	39 (6.8)	20 (8.2)	12 (6.7)	7 (4.7)	16 (8.0)	13 (6.3)	10 (6.0)
24-hour							
SBP, [a,b] mmHg	132(121-143)	127(117-138)**	133(124-143)**	136(127-148)**	133±16.5	132±17.1	132.9±15.4
DBP, [b] mmHg	76±9.6	77±9.5	76±10.0	75±9.1	75±9.5*	76±9.6*	77±9.6*
Daytime							
SBP, [a,b] mmHg	134(123-145)	129(118-141)**	135(126-144)**	140(130-150)**	135±16.6	134±17.6	135±15.3

DBP, [b] mmHg	77±10.0	77±10.0*	77±10.3*	75±9.5*	75±9.9*	77±10.1*	78±9.9*
Nighttime							
SBP, [a] mmHg	126(116-142)	120(110-134)**	131(118-142)**	135(123-149)**	127(115-144)	124(113-140)	128(117-142)
DBP, [a] mmHg	73(66-80)	74(66-81)	73(66-81)	73(67-80)	71(65-79)	73(66-80)	75(68-82)

EPVS, enlarged perivascular spaces; BG, basal ganglia; WM, white matter; BMI, body mass index; CAD, coronary artery atherosclerosis disease; TIA, transient ischemic attack; HDL, high-density lipoprotein; LDL, low-density lipoprotein; HbA1c, hemoglobin A1c; BUN, blood urea nitrogen, CCB, calcium-channel blocker; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker. * $p < 0.05$, * * $p < 0.01$.

[a]: Continuous variables with non normally distribution were expressed as median (interquartile range) and compared with Kruskal–Wallis test. [b]: Continuous variables with normal distribution were expressed as mean values±standard deviation, but with heterogeneity of variance, thus were compared with Kruskal–Wallis test.

Association between ABPV and EPVS in BG

SD and CV of ambulatory blood pressure in different categories stratified by the degree of EPVS in BG were presented in Table 2. There were statistical differences ($p < 0.05$) among the three subgroups stratified by the severity of EPVS in all of the following BPV metrics: SD and CV of SBP, CV of DBP during 24-hour, daytime and nighttime and SD of DBP during nighttime. Theses metrics gradually increased with the degree of EPVS increasing (Fig 1-3). The results of spearman correlation analysis demonstrated theses metrics were positively associated with the degree of EPVS in BG ($r>0$, $P<0.05$) (Table 3). The association between ABPV and EPVS were unchanged even after adjusting for demographic confounders (model 1), Fazekas scale (model 2) and the mean SBP or DBP during the same period (model 3), which indicated that the ABPV were independently associated with EPVS in BG. The results of ordinal logistic regression analysis were presented in Table 4.

Association between ABPV and EPVS in WM

SD and CV of ambulatory blood pressure in different categories stratified by degree of EPVS in WM were also presented in Table 2. There were statistical differences ($p <$

0.05) in SD of SBP, CV of SBP, SD of DBP and CV of DBP during 24-hour and daytime among the three categories. However, there were not linear trend among the three subgroups. The results of spearman correlation analysis showed there were no linear correlation between theses metrics and the degree of EPVS in WM (Table 3).

Table 2. Results of ABPV in all subjects and subgroups stratified by the severity of EPVS

	EPVS in BG				EPVS in WM			
	Degree 1	Degree 2	Degree 3	P	Degree 1	Degree 2	Degree 3	P
24-hour								
SD of SBP, [a] mmHg	16.6(13.8-20.2)	18.1(15.1-21.5)	18.8(15.5-23.9)	<0.001	18.2(14.7-22.8)	16.9(13.7-20.2)	17.7(15.0-21.7)	0.004
SD of DBP, [a] mmHg	11.8(9.8-14.3)	12.2(10.1-15.2)	12.5(10.1-15.3)	0.149	12.7(10.1-14.5)	11.4(9.4-14.1)	12.7(10.7-15.5)	0.001
CV of SBP, [a] %	12.9(10.4-15.3)	13.6(11.4-16.2)	14.4(11.2-17.4)	0.004	13.6(11.3-16.5)	13.2(10.3-15.5)	13.5(11.5-16.5)	0.028
CV of DBP, [a] %	15.4(12.9-19.0)	16.1(13.5-19.9)	17.3(13.8-20.2)	0.013	17.1(13.9-19.8)	15.0(12.4-18.4)	16.6(13.8-19.9)	0.001
Daytime								
SD of SBP, [a] mmHg	16.2(13.2-19.8)	17.1(14.2-21.5)	18.7(14.8-25.0)	<0.001	18.2(14.1-22.6)	16.3(13.2-19.7)	17.2(14.3-22.6)	0.004
SD of DBP, [a] mmHg	11.7(9.6-14.8)	11.8(9.5-15.0)	12.7(9.8-15.7)	0.241	12.2(9.7-15.3)	11.3(8.8-13.6)	12.6(10.2-16.0)	0.001
CV of SBP, [a] %	12.2(10.1-15.1)	12.9(10.8-16.1)	13.9(10.8-17.5)	0.005	13.3(10.6-16.7)	12.3(9.8-15.1)	13.1(10.5-16.6)	0.016
CV of DBP, [a] %	15.3(12.2-19.4)	15.1(12.7-20.5)	17.1(13.5-20.4)	0.024	16.4(13.3-20.3)	14.8(11.7-19.1)	16.3(13.2-20.4)	0.002
Nighttime								
SD of SBP, [a] mmHg	12.5(9.5-16.4)	14.8(11.0-19.0)	16.5(11.3-22.6)	<0.001	13.5(10.9-18.6)	13.4(9.8-18.9)	15.2(10.6-19.8)	0.180
SD of DBP, [a] mmHg	9.4(6.9-12.0)	10.1(7.6-13.4)	10.7(7.6-13.5)	0.010	9.9(7.3-12.6)	9.7(6.9-12.1)	10.5(7.6-13.5)	0.247
CV of SBP, [a] %	10.5(7.9-13.3)	11.1(8.4-14.4)	12.0(8.5-16.7)	0.005	10.9(8.5-14.2)	10.5(7.5-14.4)	11.6(8.4-14.6)	0.411
CV of DBP, [a] %	12.8(10.0-16.1)	13.9(11.1-17.8)	14.7(10.7-18.5)	0.003	14.3(10.7-16.9)	13.1(10.2-16.9)	13.9(10.9-18.1)	0.426

SBP: systolic blood pressure; DBP: diastolic blood pressure; CV: coefficient of

variation; SD: standard deviation.

[a]: Continuous variables with non normally distribution were expressed as median (interquartile range) and compared with Kruskal–Wallis test.

Table 3. Results of spearman correlation analysis between the degree of EPVS and ABPV

	EPVS in BG		EPVS in WM	
	r	P value	r	P value
24h				
SD of SBP	0.216	0.000	-0.013	0.762
SD of DBP	0.082	0.051	0.030	0.481
CV of SBP	0.137	0.001	-0.008	0.854
CV of DBP	0.123	0.003	-0.028	0.505
Daytime				
SD of SBP	0.205	0.000	-0.024	0.562
SD of DBP	0.065	0.120	0.031	0.459
CV of SBP	0.135	0.001	-0.023	0.585
CV of DBP	0.109	0.009	-0.017	0.679
Nighttime				
SD of SBP	0.229	0.000	0.020	0.637
SD of DBP	0.125	0.003	0.043	0.309
CV of SBP	0.136	0.001	0.027	0.521
CV of DBP	0.135	0.001	0.007	0.870

SBP: systolic blood pressure; DBP: diastolic blood pressure; CV: coefficient of variation; SD: standard deviation.

Table 4. Results of ordinal logistic regression analysis between ABPV and EPVS in BG

	Model 1		Model 2		Model 3	
	Odds ratio (95% CI)	P	Odds ratio (95% CI)	P	Odds ratio (95% CI)	P
24h						

SD of SBP	1.55 (1.32-1.83)	<0.001	1.48 (1.25-1.75)	<0.001	1.41 (1.19-1.68)	<0.001
CV of SBP	1.47 (1.19-1.83)	<0.001	1.48 (1.18-1.85)	0.001	1.60 (1.27-2.02)	<0.001
CV of DBP	1.59 (1.13-2.24)	0.008	1.69 (1.18-2.42)	0.004	1.81 (1.25-2.60)	0.001
Daytime						
SD of SBP	1.44 (1.25-1.67)	<0.001	1.39 (1.19-1.61)	<0.001	1.31 (1.12-1.54)	0.001
CV of SBP	1.32 (1.08-1.61)	0.006	1.32 (1.08-1.62)	0.008	1.43 (1.16-1.77)	0.001
CV of DBP	1.49 (1.10-2.04)	0.011	1.59 (1.15-2.19)	0.005	1.67 (1.21-2.31)	0.002
Nighttime						
SD of SBP	1.29 (1.15-1.46)	<0.001	1.25 (1.11-1.40)	<0.001	1.21 (1.07-1.37)	0.002
SD of DBP	1.39 (1.15-1.67)	<0.001	1.33 (1.11-1.61)	0.003	1.31 (1.12-1.54)	0.001
CV of SBP	1.27 (1.09-1.48)	0.002	1.26 (1.08-1.47)	0.003	1.31 (1.08-1.58)	0.006
CV of DBP	1.19 (1.04-1.36)	0.013	1.20 (1.04-1.37)	0.012	1.21 (1.05-1.39)	0.008

Results of ordinal regression analysis presented as OR per 5% increase in CV of blood pressure and 5 mmHg in SD of blood pressure.

Model1: adjusted for age, smoking, alcohol, hypertension, stroke/TIA, BUN, creatinine and using of anti-hypertensive drugs.

Model2: model 1 + Fazekas scale.

Model3: model 2 + the mean SBP or DBP during the same period.

DISCUSSION

In this study, we explored the relationship between ABPV and EPVS based on the population who presented for physical examinations. Our data suggested that all of the following metrics: SD of SBP, CV of SBP and CV of DBP during 24-hour, daytime and nighttime and SD of DBP during nighttime were positively associated with the degree of EPVS in BG. The association between the above ABPV metrics and EPVS in BG were unchanged after adjusting for demographic confounders, Fazekas scale and the mean SBP or DBP during the same period. Although there were statistical differences in ABPV metrics during 24-hour and daytime among the three subgroups stratified by EPVS severity in WM, there were no linear correlation between ABPV and the degree of EPVS in WM. In addition, we found age, Fazekas scale, hypertension, stroke/transient ischemic attack (TIA), levels of blood urea

nitrogen and creatinine were positively associated with the degree of EPVS in BG.

There were methodological strengths of our study. We recruited participants strictly according to inclusion and exclusion criteria to avoid selection bias. The patients with acute cerebrovascular and cardiovascular disorders were excluded to avoid the impact of the acute stroke, recent myocardial infarction or angina pectoris on blood pressure. The patients with a history of severe ischemic (the largest diameter of infarct size＞20mm on diffusion-weighted imaging and fluid attenuated inversion recovery) or hemorrhagic stroke were excluded because of difficulty and inaccurate assessment on EPVS. In addition, the assessments of EPVS and WMH were performed by two experienced neurologists blinded to clinical information and disagreements were resolved by consensus, which ensure the accuracy of the assessments. We collected detailed information on vascular confounders, WMH, levels of blood urea nitrogen and creatinine, which are crucial to the interpretation of EPVS[6, 20]. So we think the reliability of the data is high. There were some limitations in our study. First, our study was based on a population who visited the hospital for physical exam in a single center and the cohort may not represent the general population. According to our observation, these people had a higher economic status than that of the general population in China, and some of them showed more symptoms of anxiety. But it's regrettable that we didn't assess the anxiety symptoms by the Hamilton Anxiety Rating Scale or assess the patients' education level. Second, this was a cross-sectional study, and the causal relationship between ABPV and EPVS could not be established. Third, all participants underwent 24-hour ABPM which could only show short-term ABPV. It has been demonstrated that the prognostic significance of BPV on vascular diseases is weaker for short-term than for long-term BPV[21]. Forth, the variables were compared among three categories and the type I error was probably elevated.

This is the first study to investigate the relationship between ABPV and EPVS. Previously, several studies investigated the relationship between EPVS and hypertension. In a prospective, multicenter, hospital-based study, Zhang CQ et al[22] found hypertension was associated with the severity of EPVS in WM, not in BG. Klarenbeek P et al[23] investigated the association between ABP levels and EPVS in

first-ever lacunar stroke patients. They found higher day systolic, day diastolic and 24-hour diastolic BP levels were independently associated EPVS in BG, and no relation between ABP levels and EPVS in WM. We also analyzed the correlation between ABP levels and EPVS. We found ABP levels were associated with EPVS in BG, but not in WMH, which is consistent with Klarenbeek P et al.'s study. However, we found only SBP was positively related to higher degree of EPVS in BG in all periods, and no relation between DBP and EPVS, which are different form previous results. The different study population and different scoring methods of assessing EPVS may partly lead to the different results. Our data suggested that SD of SBP, CV of SBP and CV of DBP in all periods were positively associated with the degree of EPVS in BG, but not in WM. The present study couldn't explain the phenomenon. This may be caused by different pathogenesis of EPVS at the different locations[22, 24, 25]. Previous studies have found the anatomical structure of EPVS located in BG and WM were different[26]. The arteries in the basal ganglia are surrounded by 2 distinct coats of leptomeninges separated by a perivascular space which is continuous with the perivascular space around arteries in the subarachnoid space. Whereas there are only single periarterial layer of leptomeninges surrounding the arteries in the cerebral cortex and they penetrate into the white matter. Drainage of interstitial fluid from the brain to cervical lymph nodes may mainly go along perivascular spaces in WM rather than in BG[3, 27]. In addition, the impact of age, hypertension on EPVS seems to be stronger for EPVS located in BG than for those located in WM[24]. Similarly, the association between EPVS and the load of WMH, taken as a marker of CSVD, also appears to be stronger in BG than in WM. Thus, their dilations may present differences in terms of risk factors as well as in mechanisms in BG and WM. However, the reason SBP is related differently in these two locations remains unclear because there are a very limited number of studies on mechanisms underlying dilation of perivascular spaces in BG and WM. Several studies have demonstrated higher ABPV increased the risk of neuroimaging features of CSVD, such as WMH and lacunar infarction[14, 15]. Our results found higher ABPV was independently associated with higher degree of EPVS in BG, which support the finding that EPVS in BG are a

separate marker of CSVD.

An increased permeability of the small vessel walls and blood brain barrier (BBB) are considered to contribute to the development of EPVS, which has been reported to be associated with damage of microvascular endothelial cells and their tight junctions[1, 16, 28]. Higher ABPV would lead to more mechanical stress on the wall vessel, endothelial injury[29] and arterial stiffness[30]. Therefore, it is reasonable that high ABPV contribute to the development of EPVS by damaging endothelial cells. Our results may remind clinicians that they should pay attention to patients' ABPV and lower patients' ABPV in their clinical practices. In the future, a prospective cohort study will help better establish the relationship between ABPV and EPVS.

CONCLUSION

SD of SBP, CV of SBP and CV of DBP during all periods and SD of DBP during nighttime were positively associated with the degree of EPVS in BG. The association was unchanged after adjusting for confounders. No relation was found between ABPV and EPVS in WM. It is important for clinicians to reduce both patients' high blood pressure levels and ABPV.

Contributors WH conceived and designed the experiments. SY, WQ, LY and HF participated in the data collection. JY and YL participated in the analysis of the data. SY drafted the manuscript. WH has given final approval of the version to be published. All authors read and approved the final manuscript.

Funding This work is supported by National Natural Science Foundation of China (Grant No. 81271309).

Conflict of Interest None declared.

Ethic approval The study was approved by the Ethics Committee of Beijing Chaoyang Hospital Affiliated to Capital Medical University and was performed in accordance with the declaration of Helsinki.

Acknowledgements

The authors thank all the study participants.

Data sharing statement We agreed to share our data on request.

Reference

1. Kwee RM, Kwee TC. Virchow-robin spaces at mr imaging. *Radiographics : a review publication of the Radiological Society of North America, Inc*. 2007;27:1071-1086
2. Ozturk MH, Aydingoz U. Comparison of mr signal intensities of cerebral perivascular (virchow-robin) and subarachnoid spaces. *Journal of computer assisted tomography*. 2002;26:902-904
3. Abbott NJ. Evidence for bulk flow of brain interstitial fluid: Significance for physiology and pathology. *Neurochemistry international*. 2004;45:545-552
4. Zhu YC, Dufouil C, Mazoyer B, Soumare A, Ricolfi F, Tzourio C, Chabriat H. Frequency and location of dilated virchow-robin spaces in elderly people: A population-based 3d mr imaging study. *AJNR. American journal of neuroradiology*. 2011;32:709-713
5. Maclullich AM, Wardlaw JM, Ferguson KJ, Starr JM, Seckl JR, Deary IJ. Enlarged perivascular spaces are associated with cognitive function in healthy elderly men. *Journal of neurology, neurosurgery, and psychiatry*. 2004;75:1519-1523
6. Wardlaw JM, Smith EE, Biessels GJ, Cordonnier C, Fazekas F, Frayne R, Lindley RI, O'Brien JT, Barkhof F, Benavente OR, Black SE, Brayne C, Breteler M, Chabriat H, Decarli C, de Leeuw FE, Doubal F, Duering M, Fox NC, Greenberg S, Hachinski V, Kilimann I, Mok V, Oostenbrugge R, Pantoni L, Speck O, Stephan BC, Teipel S, Viswanathan A, Werring D, Chen C, Smith C, van Buchem M, Norrving B, Gorelick PB, Dichgans M. Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. *The Lancet. Neurology*. 2013;12:822-838
7. Doubal FN, MacLullich AM, Ferguson KJ, Dennis MS, Wardlaw JM. Enlarged perivascular spaces on mri are a feature of cerebral small vessel disease. *Stroke*. 2010;41:450-454
8. Zhu YC, Dufouil C, Soumare A, Mazoyer B, Chabriat H, Tzourio C. High degree of dilated virchow-robin spaces on mri is associated with increased risk of dementia. *Journal of Alzheimer's disease : JAD*. 2010;22:663-672
9. Berezuk C, Ramirez J, Gao F, Scott CJ, Huroy M, Swartz RH, Murray BJ, Black SE, Boulos MI. Virchow-robin spaces: Correlations with polysomnography-derived sleep parameters. *Sleep*. 2015;38:853-858
10. Ohkubo T, Hozawa A, Nagai K, Kikuya M, Tsuji I, Ito S, Satoh H, Hisamichi S, Imai Y. Prediction of stroke by ambulatory blood pressure monitoring versus screening blood pressure measurements in a general population: The ohasama study. *Journal of hypertension*. 2000;18:847-854
11. Shimada K, Kawamoto A, Matsubayashi K, Ozawa T. Silent cerebrovascular disease in the elderly. Correlation with ambulatory pressure. *Hypertension (Dallas, Tex. : 1979)*. 1990;16:692-699
12. Conen D, Bamberg F. Noninvasive 24-h ambulatory blood pressure and cardiovascular disease: A systematic review and meta-analysis. *Journal of hypertension*. 2008;26:1290-1299
13. Rothwell PM. Does blood pressure variability modulate cardiovascular risk? *Current hypertension reports*. 2011;13:177-186
14. Yamaguchi Y, Wada M, Sato H, Nagasawa H, Koyama S, Takahashi Y, Kawanami T, Kato T. Impact of ambulatory blood pressure variability on cerebral small vessel disease progression and cognitive decline in community-based elderly japanese. *American journal of hypertension*. 2014;27:1257-1267
15. Filomena J, Riba-Llena I, Vinyoles E, Tovar JL, Mundet X, Castane X, Vilar A, Lopez-Rueda

A, Jimenez-Balado J, Cartanya A, Montaner J, Delgado P. Short-term blood pressure variability relates to the presence of subclinical brain small vessel disease in primary hypertension. *Hypertension (Dallas, Tex. : 1979)*. 2015;66:634-640; discussion 445

16. Wardlaw JM, Smith C, Dichgans M. Mechanisms of sporadic cerebral small vessel disease: Insights from neuroimaging. *The Lancet. Neurology*. 2013;12:483-497

17. Groeschel S, Chong WK, Surtees R, Hanefeld F. Virchow-robin spaces on magnetic resonance images: Normative data, their dilatation, and a review of the literature. *Neuroradiology*. 2006;48:745-754

18. Yao M, Herve D, Jouvent E, Duering M, Reyes S, Godin O, Guichard JP, Dichgans M, Chabriat H. Dilated perivascular spaces in small-vessel disease: A study in cadasil. *Cerebrovascular diseases*. 2014;37:155-163

19. Fazekas F, Chawluk JB, Alavi A, Hurtig HI, Zimmerman RA. Mr signal abnormalities at 1.5 t in alzheimer's dementia and normal aging. *AJR. American journal of roentgenology*. 1987;149:351-356

20. Yamamoto Y, Ohara T, Nagakane Y, Tanaka E, Morii F, Koizumi T, Akiguchi I. Chronic kidney disease, 24-h blood pressure and small vessel diseases are independently associated with cognitive impairment in lacunar infarct patients. *Hypertension research : official journal of the Japanese Society of Hypertension*. 2011;34:1276-1282

21. Rothwell PM, Howard SC, Dolan E, O'Brien E, Dobson JE, Dahlof B, Sever PS, Poulter NR. Prognostic significance of visit-to-visit variability, maximum systolic blood pressure, and episodic hypertension. *Lancet (London, England)*. 2010;375:895-905

22. Zhang C, Chen Q, Wang Y, Zhao X, Wang C, Liu L, Pu Y, Zou X, Du W, Pan Y, Li Z, Jing J, Wang D, Luo Y, Wong KS. Risk factors of dilated virchow-robin spaces are different in various brain regions. *PloS one*. 2014;9:e105505

23. Klarenbeek P, van Oostenbrugge RJ, Lodder J, Rouhl RP, Knottnerus IL, Staals J. Higher ambulatory blood pressure relates to enlarged virchow-robin spaces in first-ever lacunar stroke patients. *Journal of neurology*. 2013;260:115-121

24. Zhu YC, Tzourio C, Soumare A, Mazoyer B, Dufouil C, Chabriat H. Severity of dilated virchow-robin spaces is associated with age, blood pressure, and mri markers of small vessel disease: A population-based study. *Stroke*. 2010;41:2483-2490

25. Satizabal CL, Zhu YC, Dufouil C, Tzourio C. Inflammatory proteins and the severity of dilated virchow-robin spaces in the elderly. *Journal of Alzheimer's disease : JAD*. 2013;33:323-328

26. Pollock H, Hutchings M, Weller RO, Zhang ET. Perivascular spaces in the basal ganglia of the human brain: Their relationship to lacunes. *Journal of anatomy*. 1997;191 (Pt 3):337-346

27. Weller RO, Subash M, Preston SD, Mazanti I, Carare RO. Perivascular drainage of amyloid-beta peptides from the brain and its failure in cerebral amyloid angiopathy and alzheimer's disease. *Brain pathology (Zurich, Switzerland)*. 2008;18:253-266

28. Wuerfel J, Haertle M, Waiczies H, Tysiak E, Bechmann I, Wernecke KD, Zipp F, Paul F. Perivascular spaces--mri marker of inflammatory activity in the brain? *Brain : a journal of neurology*. 2008;131:2332-2340

29. Diaz KM, Veerabhadrappa P, Kashem MA, Thakkar SR, Feairheller DL, Sturgeon KM, Ling C, Williamson ST, Kretzschmar J, Lee H, Grimm H, Babbitt DM, Vin C, Fan X, Crabbe DL, Brown MD. Visit-to-visit and 24-h blood pressure variability: Association with endothelial

and smooth muscle function in african americans. *Journal of human hypertension*. 2013;27:671-677

30. Schillaci G, Bilo G, Pucci G, Laurent S, Macquin-Mavier I, Boutouyrie P, Battista F, Settimi L, Desamericq G, Dolbeau G, Faini A, Salvi P, Mannarino E, Parati G. Relationship between short-term blood pressure variability and large-artery stiffness in human hypertension: Findings from 2 large databases. *Hypertension (Dallas, Tex. : 1979)*. 2012;60:369-377

Figure 1. The ABPV metrics of subgroups stratified by EPVS severity in BG during 24-hour. (a) CV of systolic blood pressure. (b) CV of diastolic blood pressure. (c) SD of systolic blood pressure. (d) SD of diastolic blood pressure.

Figure 2. The ABPV metrics of subgroups stratified by EPVS severity in BG during daytime. (a) CV of systolic blood pressure. (b) CV of diastolic blood pressure. (c) SD of systolic blood pressure. (d) SD of diastolic blood pressure.

Figure 3. The ABPV metrics of subgroups stratified by EPVS severity in BG during nighttime. (a) CV of systolic blood pressure. (b) CV of diastolic blood pressure. (c) SD of systolic blood pressure. (d) SD of diastolic blood pressure.

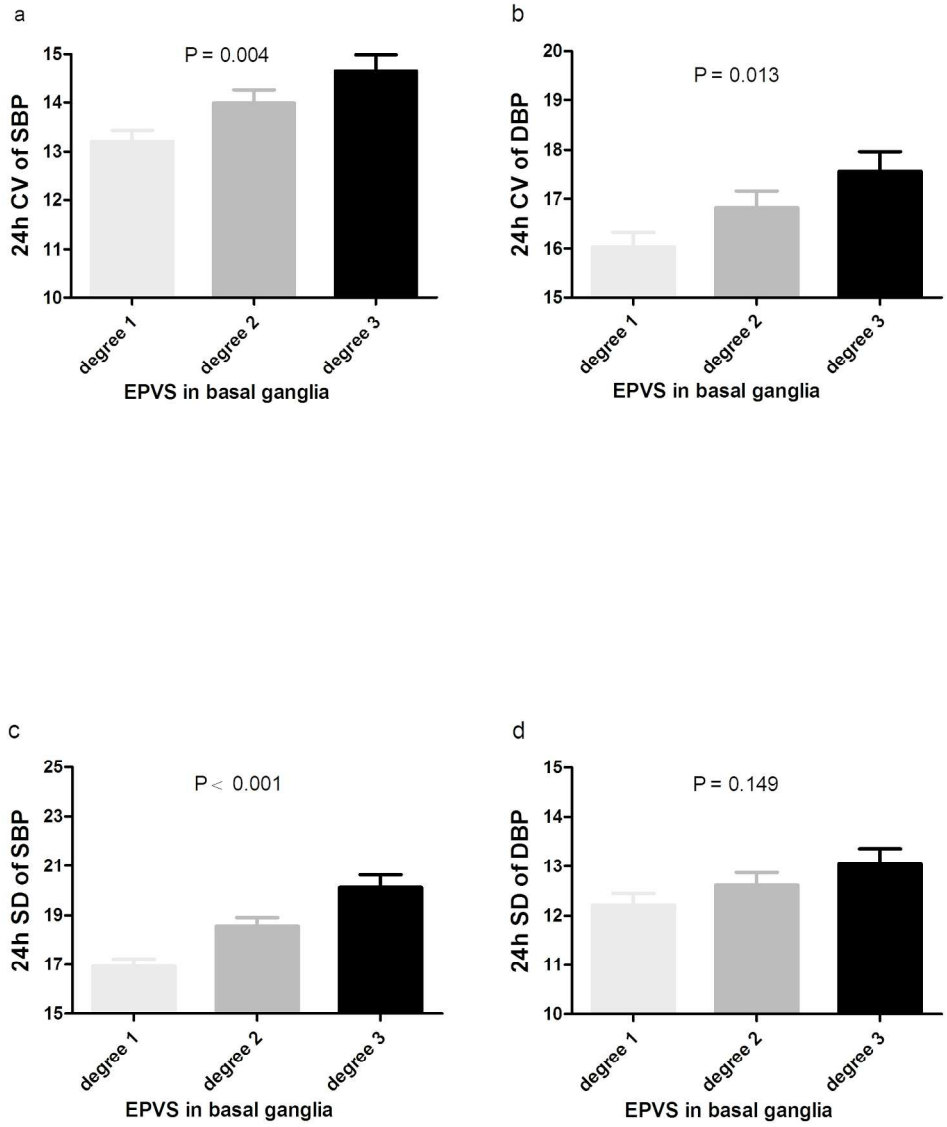


Figure 1. The ABPV metrics of subgroups stratified by EPVS severity in BG during 24-hour. (a) CV of systolic blood pressure. (b) CV of diastolic blood pressure. (c) SD of systolic blood pressure. (d) SD of diastolic blood pressure.

191x228mm (300 x 300 DPI)

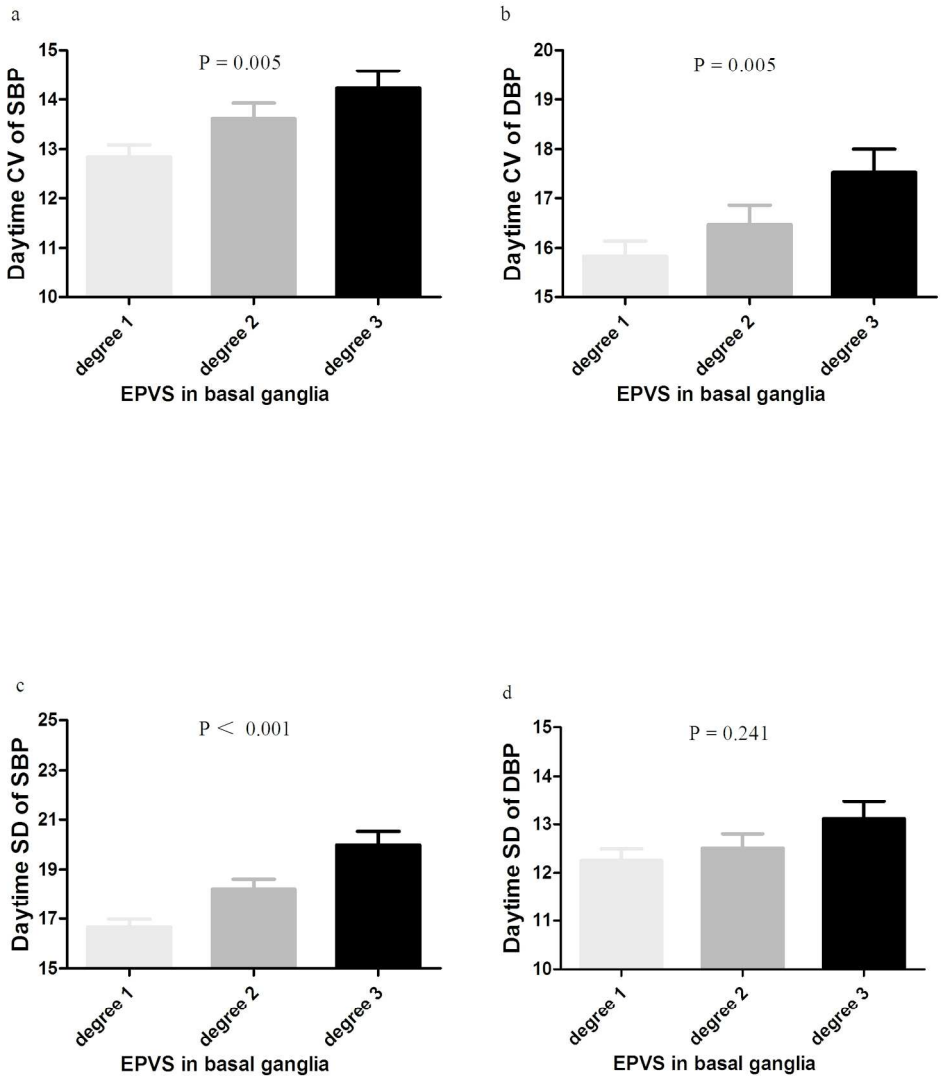


Figure 2. The ABPV metrics of subgroups stratified by EPVS severity in BG during daytime. (a) CV of systolic blood pressure. (b) CV of diastolic blood pressure. (c) SD of systolic blood pressure. (d) SD of diastolic blood pressure.

190x218mm (300 x 300 DPI)

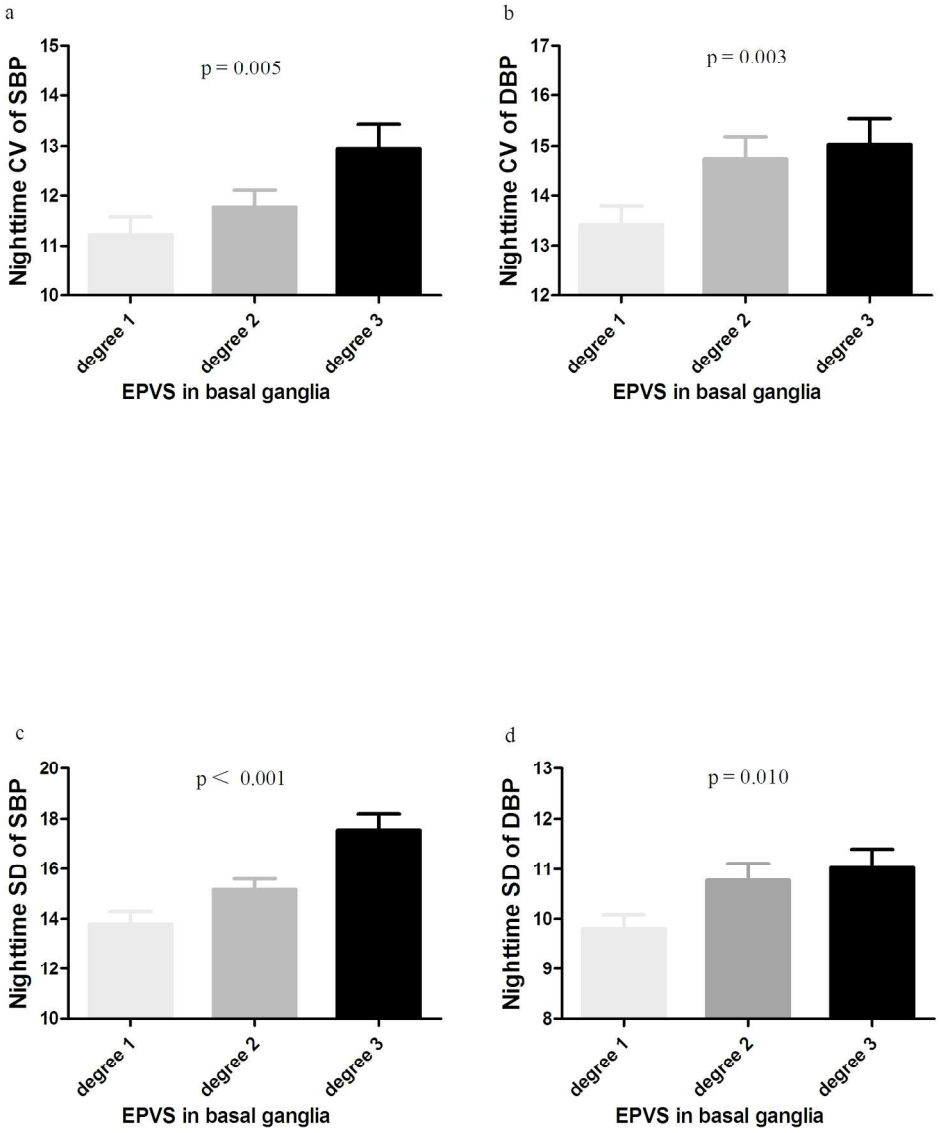
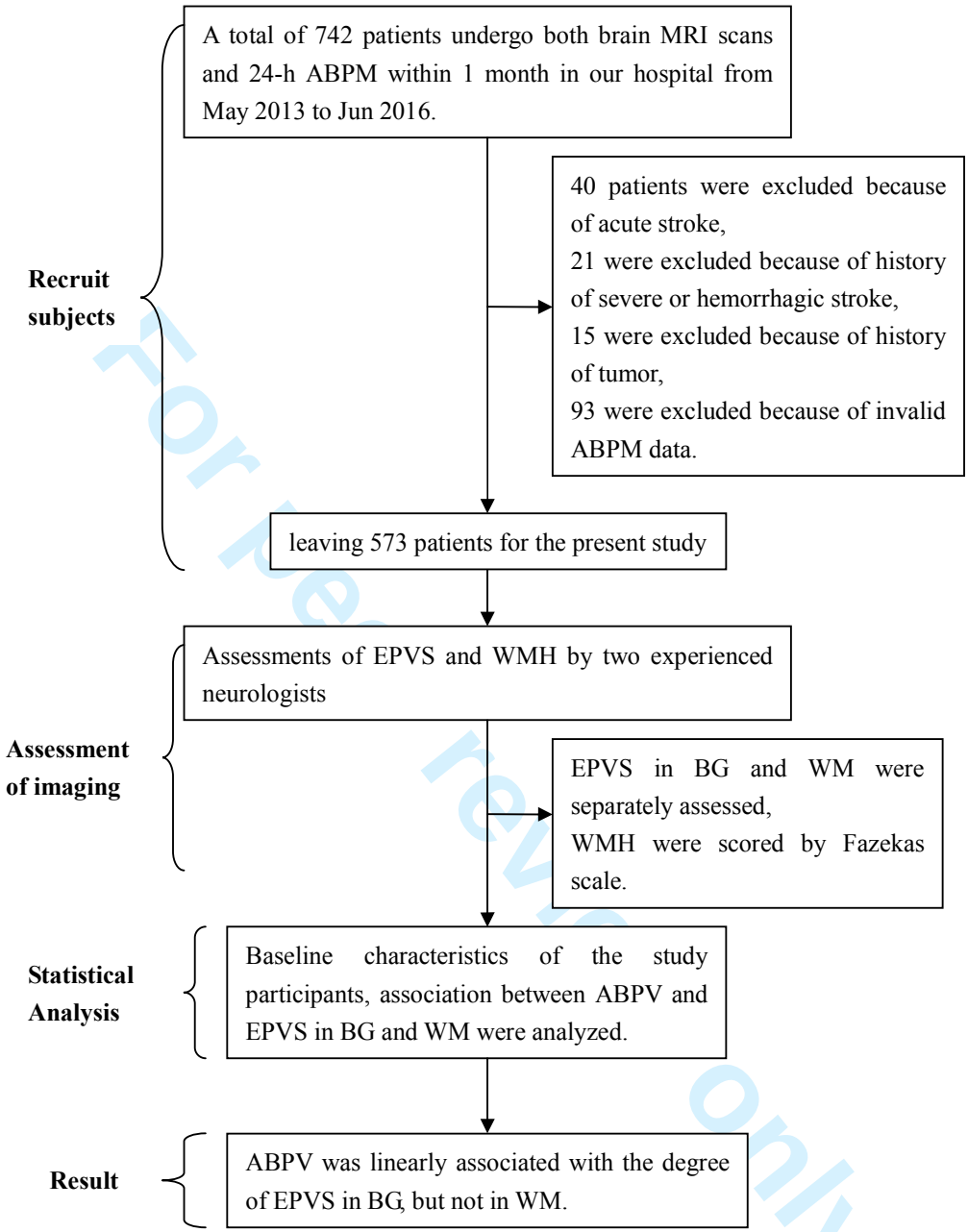


Figure 3. The ABPV metrics of subgroups stratified by EPVS severity in BG during nighttime. (a) CV of systolic blood pressure. (b) CV of diastolic blood pressure. (c) SD of systolic blood pressure. (d) SD of diastolic blood pressure.

189x227mm (300 x 300 DPI)

The comparison of general clinical characteristics between the included and excluded participants

Characteristics	enrolled patients	excluded patients	P
n	573	169	-
Age, years	67.8±14.8	69.6±9.6	0.443
Sex, male (%)	355 (62.0)	101(59.8)	0.607
Current smoking (%)	162 (28.3)	55(32.5)	0.283
Current alcohol (%)	126 (22.0)	42(24.9)	0.435
Hypertension (%)	420 (73.3)	115(68.0)	0.181
Diabetes (%)	191 (33.3)	44(26.0)	0.073
coronary atherosclerosis disease (%)	140 (24.4)	35(20.7)	0.316
body mass index, kg/m^2	25.6±3.5	25.1±3.0	0.160
Using of anti-hypertensive drugs (%)	342 (59.7)	99(58.6)	0.797



ABPM, ambulatory blood pressure monitoring; EPVS, enlarged perivascular spaces; WMH, white matter hyperintensities; BG, basal ganglia; WM, white matter.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	P1 and 2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	P2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	P3-4
Objectives	3	State specific objectives, including any prespecified hypotheses	P4
Methods			
Study design	4	Present key elements of study design early in the paper	P4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	P4
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	P4
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	P5-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	P5-6
Bias	9	Describe any efforts to address potential sources of bias	P4 and 5

Study size	10	Explain how the study size was arrived at	P4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	P6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	P6
		(*b*) Describe any methods used to examine subgroups and interactions	P6
		(*c*) Explain how missing data were addressed	P6
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	P6
		(b) Give reasons for non-participation at each stage	P6
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	P7
		(b) Indicate number of participants with missing data for each variable of interest	P7
Outcome data	15*	Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	P6-12
		(*b*) Report category boundaries when continuous variables were categorized	

		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	P12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	P12-13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	P13-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	P14-15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	P15

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

The relationship between ambulatory blood pressure variability and enlarged perivascular spaces: a cross-sectional study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2016-015719.R4
Article Type:	Research
Date Submitted by the Author:	04-Jul-2017
Complete List of Authors:	Yang, Shuna; Beijing Chaoyang Hospital, Neurology Qin, Wei; Beijing Chaoyang Hospital, Neurology Yang, Lei; Beijing Chaoyang Hospital, Neurology Fan, Huimin; Beijing Chaoyang Hospital, Neurology Li, Yue; Beijing Chaoyang Hospital, Neurology Yin, Jiangmei; Beijing Chaoyang Hospital, Neurology Hu, Wenli; Neurology
Primary Subject Heading:	Neurology
Secondary Subject Heading:	Health services research, Neurology
Keywords:	cerebral small vessel disease, enlarged perivascular spaces, Virchow-Robin spaces, blood pressure variability, ambulatory blood pressure monitoring

The relationship between ambulatory blood pressure variability and enlarged perivascular spaces: a cross-sectional study

Shuna Yang[1], Wei Qin[1], Lei Yang[1], Huimin Fan[1], Yue Li[1], Jiangmei Yin[1], Wenli Hu[1*]

1: Department of Neurology, Beijing Chaoyang Hospital, Capital Medical University, Beijing, China

*: Corresponding Author

Email: huwenli@sina.com, Telephone: +8601085231376, Fax: 011-86-10-65926388

Institution address: Beijing Chaoyang Hospital, No.8 South Gongti Road, Chaoyang District, Beijing, China

Abstract

Objectives: Recent studies reported that 24-hour ambulatory blood pressure variability (ABPV) was associated with lacunar infarction and white matter hyperintensities (WMH). However, the relationship between ABPV and enlarged perivascular spaces (EPVS) hasn't been investigated. Thus, our study aimed to investigate whether ABPV is associated with EPVS by 24-hour ambulatory blood pressure monitoring (ABPM).

Design: We conducted this study as a cross-sectional study.

Settings: The study was based on patients who presented for physical examinations in our hospital from May 2013 to Jun 2016.

Participants: Patients with both brain MRI scans and 24-hour ABPM were included and patients with acute stroke, a history of severe stroke and some other severe diseases were excluded. A total of 573 Chinese patients were prospectively enrolled in this study.

Primary and secondary outcome measures: EPVS in basal ganglia (BG) and white matter (WM) were identified on MRI and classified into three categories by the severity. WMH were scored by Fazekas scale. Coefficient of variation (CV) and standard deviation (SD) were considered as metrics of ABPV. Spearman correlation analysis and ordinal logistic regression analysis were used to assess the relationship between ABPV and EPVS.

Results: There were statistical differences among the subgroups stratified by the severity of EPVS in BG in the following ABPV metrics: SD and CV of systolic blood pressure (SBP), CV of diastolic blood pressure (DBP) in 24-hour, daytime and nighttime and SD of DBP in nighttime. The above ABPV metrics were positively associated with the degree of EPVS. The association was unchanged after adjusting for confounders. Spearman correlation analysis showed ABPV wasn't related to the degree of EPVS in WM.

Conclusion: ABPV was independently associated with EPVS in BG after controlling for blood pressure, but not in WM. Pathogenesis of EPVS in BG and WM might be different.

Keywords cerebral small vessel disease, enlarged perivascular spaces, Virchow-Robin spaces, blood pressure variability, ambulatory blood pressure monitoring

Strengths and limitations of this study

- Assessments of EPVS and WMH were performed by two experienced neurologists blinded to clinical information and disagreements were resolved by consensus, which ensure the accuracy of the assessments.
- Detailed information on some confounders crucial to the interpretation of EPVS was collected and ordinal logistic regression analysis was performed to determine the independency of association.
- The study was based on a population who presented to the hospital for physical exam in a single center and the cohort may not represent the general population.
- This was a cross-sectional study, and the causal relationship between ABPV and EPVS could not be established.

INTRODUCTION

Perivascular spaces, or Virchow-Robin spaces, are perivascular compartments surrounding the small penetrating cerebral vessels, serving as an important drainage system for interstitial fluids and solute in the brain[1]. They can dilate with accumulation of the interstitial fluids[2, 3]. Enlarged perivascular spaces (EPVS) appear as punctate or linear signal intensities similar to cerebrospinal fluids (CSF) on all MRI sequences in white matter (WM), basal ganglia (BG), hippocampus and brainstem[4, 5]. Recent studies indicated that EPVS were a magnetic resonance imaging (MRI) marker of cerebral small vessel diseases (CSVD) and were associated with other morphological features of CSVD such as white matter hyperintensities (WMH) and lacunes[6, 7]. Some studies found EPVS were associated with impaired cognitive function[5], incident dementia[8] and sleep disorders[9]. Therefore, it is of clinical importance to understand the risk factors for EPVS and search for treatable options in the future.

24-hour ambulatory blood pressure monitoring (ABPM) is proven to be a more useful and scientific method to predict blood pressure-related brain damage than single

office blood pressure measurement[10, 11]. Ambulatory blood pressure variability (ABPV) could be well documented by 24-hour ABPM. Previous studies demonstrated higher ABPV increased the risk of cardiovascular events[12, 13], WMH, lacunar infarction, and cognitive decline[14, 15]. WMH, lacunar infarction and EPVS are all neuroimaging features of CSVD and share some risk factors, such as age and hypertension[16]. However, the relationship between ABPV and EPVS has never been investigated. Thus in the present study, we aimed to investigate whether ABPV, which was reflected by 24-hour ABPM, was independently associated with EPVS.

METHODS

Study subjects

We conducted this study as a cross-sectional study. The inpatients for physical examinations in Medicine Department and Neurology Department of Beijing Chaoyang Hospital Affiliated to Capital Medical University were prospectively identified from May 2013 to Jun 2016. Some of them had a history of hypertension, diabetes mellitus, lacunar stroke or other risk factors for vascular diseases. They worried about the cerebrovascular diseases and wanted a well check up. They were screened according to our inclusion and exclusion criteria. The number of arriving patients during the study period, inclusion and exclusion criteria determined the sample size. Inclusion criteria were: (1) patients underwent both brain MRI scans and 24-hour ABPM within 1 month; (2) patients agreed to participate in our study and signed an informed consent. The following patients were excluded: (1) patients with acute stroke, Parkinson disease, dementia, severe traumatic or toxic or infectious brain injury, and brain tumor; (2) patients with severe heart disease, recent myocardial infarction or angina pectoris disorders, severe infections, severe nephrosis or liver disease, thrombotic diseases and tumor; (3) patients with history of severe ischemic (the largest diameter of infarct size＞20mm on diffusion-weighted imaging and fluid attenuated inversion recovery) or hemorrhagic stroke because of difficulty assessments on EPVS; (4) patients with invalid 24-hour ABPM data (The 24-h ABPM data were considered invalid if measurement times was < 70%, or < 1

measurement per hour during daytime, or < 6 in total during nighttime).

Assessments of EPVS and WMH

The neurological image examinations were performed in Radiology Department of our hospital. MR images were acquired on a 3.0 T MR scanner (Siemens, Erlangen, Germany).

EPVS were defined as CSF-like signal intensity lesions of round, ovoid, or linear shape of < 3mm and located in areas supplied by perforating arteries[6, 17]. We distinguished lacune from EPVS by their larger size (> 3mm), spheroid shape and surrounding hyperintensities on FLAIR. WMH were defined as hyperintense signals on T2-weighted and FLAIR and decreased signal intensities on T1-weighted MR imaging.

EPVS in BG and WM were separately assessed according to the scales which were used in other studies[18]. In BG, EPVS were rated according to the number in the slice containing the maximum amount of EPVS. The grades of EPVS were rated as following: grade 1: < 5 EPVS, grade 2: 5 to 10 EPVS, grade 3: 10 to 20 EPVS, and grade 4: > 20 EPVS. In WM, EPVS were scored as follows: grade 1：<10 EPVS in total WM, grade 2：>10 in total WM and <10 in the slice containing the maximum number of EPVS, grade 3：10 to 20 EPVS in the slice containing the maximum number of EPVS, grade 4：> 20 in the slice containing the maximum number of EPVS. We classified EPVS into three categories: degree 1 = grade 1; degree 2 = grade 2; degree 3 = grade 3 and 4.

WMH were scored by Fazekas scale. The detailed description of assessments has been previously published[19]. Periventricular and deep WMH were evaluated separately and then added together as Fazekas scores.

The intrarater agreement for the rating of EPVS and WMH was assessed on a random sample of 100 individuals with a month interval between the first and second readings. Assessments of EPVS and WMH were performed by two experienced neurologists blinded to clinical information to avoid bias. Random scans of 100 individuals were independently examined by the two experienced neurologists blinded to each other's readings. The *k* statistics of intrarater and interrater agreement was 0.80 or above,

indicating good reliability. Disagreement was resolved by discussing with other co-authors.

24-hour ambulatory blood pressure monitoring

24-hour ABPM was performed using an automated system (FB-250; Fukuda Denshi, Tokyo, Japan). BP was measured every 30 minutes during the daytime (8:00 AM to 11:00 PM) and every 60 minutes during the nighttime (11:00 PM to 8:00 AM). We excluded a 2-hour transition period around the reported rising and retiring times. The mean systolic blood pressure (SBP), diastolic blood pressure (DBP), coefficient of variation (CV) and standard deviation (SD) of SBP and DBP during 24-hour, daytime, and nighttime were collected. The CV value was defined as the ratio between the SD and the mean SBP or DBP at the same periods. SD and CV were considered as metrics of BPV in this study. Patients continued taking their previous medications, and we registered the use of anti-hypertension drugs.

Statistical analysis

Continuous variables were summarized as mean values ± standard deviation (SD) or median (interquartile range) according to whether its distribution conformed to a normal distribution. Analysis of variance (ANOVA) was used for comparison of continuous variables with both normal distribution and homogeneity of variance, whereas were compared with Kruskal–Wallis test as appropriate. Categorical variables were presented as absolute numbers and percentages. Chi-squared test was used for comparison of categorical variables. Spearman correlation analysis was used to calculate the association between ABPV and the severity of EPVS. The proportional odds assumption was met, thus ordinal logistic regression analysis was performed to determine whether the ABPV was independently associated with EPVS after adjusting for demographic confounders (model 1), Fazekas scale (model 2) and the mean SBP or DBP during the same period (model 3). The results were based on valid data; missing data were excluded. Analyses were performed with Statistical Package for Social Sciences (SPSS version21.0), and statistical significance was accepted at the $p < 0.05$.

RESULTS

Baseline characteristics of the study participants

742 patients underwent both brain MRI scans and 24-hour ABPM within 1 month in the Medicine Department or Neurology Department of our hospital from May 2013 to Jun 2016. 40 patients were excluded because of acute stroke, 21 were excluded because of history of severe or hemorrhagic stroke, 15 were excluded because of a history of tumor and 93 were excluded because of invalid ABPM data, leaving 573 patients enrolled in the present study. None of them had missing data. There were no statistical differences ($P>0.05$) in age, body mass index, proportion of male, current smoking, current alcohol, diabetes, hypertension, coronary artery atherosclerosis disease and using of anti-hypertensive drugs between the excluded subjects and the final group (Supplementary file). Table 1 showed the characteristics of all enrolled subjects and subgroups stratified by the degree of EPVS in different brain regions. Age, Fazekas scale, proportion of hypertension and stroke/TIA, levels of blood urea nitrogen and creatinine increased with the degree of EPVS in BG increasing. There were statistical differences in age, Fazekas scale and proportion of coronary artery atherosclerosis disease (CAD) among subgroups based on the degree of EPVS in WM.

Table 1. General characteristics of all enrolled subjects and each EPVS category stratified by the severity of EPVS

Characteristics	All patients	EPVS in basal ganglia			EPVS in white matter		
		Degree 1	Degree 2	Degree 3	Degree 1	Degree 2	Degree 3
n (%)	573	244 (42.6%)	179 (31.2%)	150 (26.2%)	200 (34.9%)	207 (36.1%)	166 (29.0%)
Age, [a] years	69(55-81)	58(51-74)**	68(57-80)**	80(73-85)**	75(57-83)**	66(55-78)**	66(54-80)**
Sex, male (%)	355 (62.0)	143 (58.6)	108 (60.3)	104 (69.3)	115 (57.5)	128 (61.8)	112 (67.5)
Current smoking (%)	162 (28.3)	83 (34.0)*	61(34.1)*	18(12.0)*	52 (26.0)	60 (29.0)	50 (30.1)
Current alcohol (%)	126 (22.0)	62 (25.4)*	45 (25.1)*	19 (12.7)*	36 (18.0)	50 (24.2)	40 (24.1)
Hypertension (%)	420 (73.3)	170 (69.7)*	122 (68.2)*	128 (85.3)*	150 (75.0)	145 (70.5)	125 (74.7)
Diabetes (%)	191 (33.3)	78 (32.0)	59 (33.0)	54 (36.0)	71 (35.5)	62 (30.0)	58 (34.9)
CAD (%)	140 (24.4)	48 (19.7)	48 (26.8)	44 (29.3)	61 (30.5) *	45 (21.7) *	34 (20.5) *

Stroke or TIA (%)	125 (21.8)	40 (16.4)**	33 (18.4)**	52 (34.7)**	49 (24.5)	39 (18.8)	37 (22.2)
BMI, [b]kg/m^2	25.6±3.5	25.6±3.4	25.3±3.5	25.8±3.5	25.8±3.4	25.4±3.5	25.5±3.5
HDL, [a] mmol/L	1.16(1.00-1.38)	1.15(0.99-1.37)	1.17(0.98-1.41)	1.17(1.00-1.32)	1.17(1.00-1.38)	1.15(0.98-1.37)	1.15(0.99-1.34)
LDL, [a] mmol/L	2.40(1.90-2.94)	2.42(1.96-3.00)	2.47(1.88-2.93)	2.20(1.79-2.91)	2.32(1.88-2.94)	2.29(1.81-2.90)	2.51(2.00-3.00)
HbA1, [a] %	6.0(5.7-6.7)	6.0(5.7-6.7)	6.0(5.7-6.7)	6.1(5.7-6.7)	6.1(5.7-6.8)	6.0(5.7-6.6)	6.0(5.7-6.8)
BUN, [a] mmol/L	5.46(4.46-6.70)	5.18(4.34-6.34)**	5.36(4.32-6.59)**	5.97(4.82-7.42)**	5.50(4.55-7.02)	5.39(4.36-6.39)	5.42(4.50-6.81)
Creatinine, [a] umol/L	74.2(62.8-89.2)	70.2(59.7-84.6)**	74.5(63.7-89.6)**	81.9(66.4-94.1)**	77.0(62.8-92.1)	72.5(61.5-87.0)	74.0(62.9-89.1)
Fazekas scale [a]	3(2-5)	2(1-3)**	3(2-4)**	5(4-6)**	3(2-6)**	2(2-4)**	3(2-4)**
Using of anti-hypertensive drugs (%)	342 (59.7)	130 (53.3) *	96 (53.6) *	116 (77.3) *	129 (64.5)	114 (55.1)	99 (59.6)
Class of anti-hypertensive drugs							
Dihydropyridinic CCB (%)	226 (39.4)	74 (30.3)	67 (37.4)	63 (42.0)	69 (34.5)	79 (38.2)	55 (33.1)
ACEI (%)	26 (4.5)	11 (4.5)	6 (3.4)	9 (6.0)	8 (4.0)	9 (4.3)	9 (5.7)
ARB (%)	160 (27.9)	70 (28.7)	46 (25.7)	44 (29.3)	69 (34.5) *	52 (25.1) *	39 (23.5) *
β-Blockers (%)	96 (16.8)	34 (13.9)	28 (15.6)	34 (22.7)	40 (20.0)	31 (15.0)	25 (15.1)
Nonloop diuretics (%)	39 (6.8)	20 (8.2)	12 (6.7)	7 (4.7)	16 (8.0)	13 (6.3)	10 (6.0)

EPVS, enlarged perivascular spaces; BMI, body mass index; CAD, coronary artery atherosclerosis disease; TIA, transient ischemic attack; HDL, high-density lipoprotein; LDL, low-density lipoprotein; HbA1c, hemoglobin A1c; BUN, blood urea nitrogen, CCB, calcium-channel blocker; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker. * $p < 0.05$, * * $p < 0.01$.

[a]: Continuous variables with non normally distribution were expressed as median (interquartile range) and compared with Kruskal–Wallis test. [b]: Continuous variables with normal distribution were expressed as mean values±standard deviation, but with heterogeneity of variance, thus were compared with Kruskal–Wallis test.

Ambulatory blood pressure levels for each EPVS category were presented in Table 2. There were statistical differences in the mean SBP during 24-hour, daytime, and nighttime among the categories stratified by the degree of EPVS in BG. The results of spearman correlation analysis showed SBP was positively related to higher degree of

EPVS in BG during all periods (SBP of 24-hour: r=0.23, p < 0.01; SBP of daytime: r=0.25, p < 0.01; SBP of nighttime: r=0.30, p < 0.01). The mean DBP of daytime and nighttime increased with the degree of EPVS in WMH increasing. However, the results of spearman correlation analysis showed that DBP levels were not associated with higher numbers of EPVS in WM (p > 0.05).

Table 2. Ambulatory blood pressure levels of all enrolled subjects and each EPVS category stratified by the severity of EPVS

Characteristics	All patients	EPVS in basal ganglia			EPVS in white matter		
		Degree 1	Degree 2	Degree 3	Degree 1	Degree 2	Degree 3
24-hour							
SBP, [a,b] mmHg	132(121-143)	127(117-138)**	133(124-143)**	136(127-148)**	133±16.5	132±17.1	132.9±15.4
DBP, [b] mmHg	76±9.6	77±9.5	76±10.0	75±9.1	75±9.5*	76±9.6*	77±9.6*
Daytime							
SBP, [a,b] mmHg	134(123-145)	129(118-141)**	135(126-144)**	140(130-150)**	135±16.6	134±17.6	135±15.3
DBP, [b] mmHg	77±10.0	77±10.0*	77±10.3*	75±9.5*	75±9.9*	77±10.1*	78±9.9*
Nighttime							
SBP, [a] mmHg	126(116-142)	120(110-134)**	131(118-142)**	135(123-149)**	127(115-144)	124(113-140)	128(117-142)
DBP, [a] mmHg	73(66-80)	74(66-81)	73(66-81)	73(67-80)	71(65-79)	73(66-80)	75(68-82)

EPVS, enlarged perivascular spaces; SBP, systolic blood pressure; DBP, diastolic blood pressure. * $p < 0.05$, * * $p < 0.01$

[a]: Continuous variables with non normally distribution were expressed as median (interquartile range) and compared with Kruskal–Wallis test. [b]: Continuous variables with normal distribution were expressed as mean values ± standard deviation, but with heterogeneity of variance, thus were compared with Kruskal–Wallis test.

Association between ABPV and EPVS in BG

SD and CV of ambulatory blood pressure in different categories stratified by the degree of EPVS in BG were presented in Table 3. There were statistical differences ($p < 0.05$) among the three subgroups stratified by the severity of EPVS in all of the following BPV metrics: SD and CV of SBP, CV of DBP during 24-hour, daytime and

nighttime and SD of DBP during nighttime. Theses metrics gradually increased with the degree of EPVS increasing (Fig 1-3). The results of spearman correlation analysis demonstrated theses metrics were positively associated with the degree of EPVS in BG ($r>0$, $P<0.05$). The association between ABPV and EPVS were unchanged even after adjusting for demographic confounders (model 1), Fazekas scale (model 2) and the mean SBP or DBP during the same period (model 3), which indicated that the ABPV were independently associated with EPVS in BG. The results of ordinal logistic regression analysis were presented in Table 4.

Association between ABPV and EPVS in WM

SD and CV of ambulatory blood pressure in different categories stratified by degree of EPVS in WM were also presented in Table 3. There were statistical differences ($p < 0.05$) in SD of SBP, CV of SBP, SD of DBP and CV of DBP during 24-hour and daytime among the three categories. However, there were not linear trend among the three subgroups. The results of spearman correlation analysis showed there were no linear correlation between theses metrics and the degree of EPVS in WM ($P>0.05$).

Table 3. Results of ABPV in all subjects and subgroups stratified by the severity of EPVS

	EPVS in BG				EPVS in WM			
	Degree 1	Degree 2	Degree 3	P	Degree 1	Degree 2	Degree 3	P
24-hour								
SD of SBP, [a] mmHg	16.6(13.8-20.2)	18.1(15.1-21.5)	18.8(15.5-23.9)	<0.001	18.2(14.7-22.8)	16.9(13.7-20.2)	17.7(15.0-21.7)	0.004
SD of DBP, [a] mmHg	11.8(9.8-14.3)	12.2(10.1-15.2)	12.5(10.1-15.3)	0.149	12.7(10.1-14.5)	11.4(9.4-14.1)	12.7(10.7-15.5)	0.001
CV of SBP, [a] %	12.9(10.4-15.3)	13.6(11.4-16.2)	14.4(11.2-17.4)	0.004	13.6(11.3-16.5)	13.2(10.3-15.5)	13.5(11.5-16.5)	0.028
CV of DBP, [a] %	15.4(12.9-19.0)	16.1(13.5-19.9)	17.3(13.8-20.2)	0.013	17.1(13.9-19.8)	15.0(12.4-18.4)	16.6(13.8-19.9)	0.001
Daytime								
SD of SBP, [a] mmHg	16.2(13.2-19.8)	17.1(14.2-21.5)	18.7(14.8-25.0)	<0.001	18.2(14.1-22.6)	16.3(13.2-19.7)	17.2(14.3-22.6)	0.004
SD of DBP, [a] mmHg	11.7(9.6-14.8)	11.8(9.5-15.0)	12.7(9.8-15.7)	0.241	12.2(9.7-15.3)	11.3(8.8-13.6)	12.6(10.2-16.0)	0.001

CV of SBP, [a] %	12.2(10.1-15.1)	12.9(10.8-16.1)	13.9(10.8-17.5)	0.005	13.3(10.6-16.7)	12.3(9.8-15.1)	13.1(10.5-16.6)	0.016
CV of DBP, [a] %	15.3(12.2-19.4)	15.1(12.7-20.5)	17.1(13.5-20.4)	0.024	16.4(13.3-20.3)	14.8(11.7-19.1)	16.3(13.2-20.4)	0.002
Nighttime								
SD of SBP, [a] mmHg	12.5(9.5-16.4)	14.8(11.0-19.0)	16.5(11.3-22.6)	<0.001	13.5(10.9-18.6)	13.4(9.8-18.9)	15.2(10.6-19.8)	0.180
SD of DBP, [a] mmHg	9.4(6.9-12.0)	10.1(7.6-13.4)	10.7(7.6-13.5)	0.010	9.9(7.3-12.6)	9.7(6.9-12.1)	10.5(7.6-13.5)	0.247
CV of SBP, [a] %	10.5(7.9-13.3)	11.1(8.4-14.4)	12.0(8.5-16.7)	0.005	10.9(8.5-14.2)	10.5(7.5-14.4)	11.6(8.4-14.6)	0.411
CV of DBP, [a] %	12.8(10.0-16.1)	13.9(11.1-17.8)	14.7(10.7-18.5)	0.003	14.3(10.7-16.9)	13.1(10.2-16.9)	13.9(10.9-18.1)	0.426

SBP: systolic blood pressure; DBP: diastolic blood pressure; CV: coefficient of variation; SD: standard deviation.

[a]: Continuous variables with non normally distribution were expressed as median (interquartile range) and compared with Kruskal–Wallis test.

Table 4. Results of ordinal logistic regression analysis between ABPV and EPVS in BG

	Model 1		Model 2		Model 3	
	Odds ratio (95% CI)	P	Odds ratio (95% CI)	P	Odds ratio (95% CI)	P
24h						
SD of SBP	1.55 (1.32-1.83)	<0.001	1.48 (1.25-1.75)	<0.001	1.41 (1.19-1.68)	<0.001
CV of SBP	1.47 (1.19-1.83)	<0.001	1.48 (1.18-1.85)	0.001	1.60 (1.27-2.02)	<0.001
CV of DBP	1.59 (1.13-2.24)	0.008	1.69 (1.18-2.42)	0.004	1.81 (1.25-2.60)	0.001
Daytime						
SD of SBP	1.44 (1.25-1.67)	<0.001	1.39 (1.19-1.61)	<0.001	1.31 (1.12-1.54)	0.001
CV of SBP	1.32 (1.08-1.61)	0.006	1.32 (1.08-1.62)	0.008	1.43 (1.16-1.77)	0.001
CV of DBP	1.49 (1.10-2.04)	0.011	1.59 (1.15-2.19)	0.005	1.67 (1.21-2.31)	0.002
Nighttime						
SD of SBP	1.29 (1.15-1.46)	<0.001	1.25 (1.11-1.40)	<0.001	1.21 (1.07-1.37)	0.002
SD of DBP	1.39 (1.15-1.67)	<0.001	1.33 (1.11-1.61)	0.003	1.31 (1.12-1.54)	0.001
CV of SBP	1.27 (1.09-1.48)	0.002	1.26 (1.08-1.47)	0.003	1.31 (1.08-1.58)	0.006

CV of DBP	1.19 (1.04-1.36)	0.013	1.20 (1.04-1.37)	0.012	1.21 (1.05-1.39)	0.008

Results of ordinal regression analysis presented as OR per 5% increase in CV of blood pressure and 5 mmHg in SD of blood pressure.

Model1: adjusted for age, smoking, alcohol, hypertension, stroke/TIA, BUN, creatinine and using of anti-hypertensive drugs.

Model2: model 1 + Fazekas scale.

Model3: model 2 + the mean SBP or DBP during the same period.

DISCUSSION

In this study, we explored the relationship between ABPV and EPVS based on the population who presented for physical examinations. Our data suggested that all of the following metrics: SD of SBP, CV of SBP and CV of DBP during 24-hour, daytime and nighttime and SD of DBP during nighttime were positively associated with the degree of EPVS in BG. The association between the above ABPV metrics and EPVS in BG were unchanged after adjusting for demographic confounders, Fazekas scale and the mean SBP or DBP during the same period. Although there were statistical differences in ABPV metrics during 24-hour and daytime among the three subgroups stratified by EPVS severity in WM, there were no linear correlation between ABPV and the degree of EPVS in WM. In addition, we found age, Fazekas scale, hypertension, stroke/transient ischemic attack (TIA), levels of blood urea nitrogen and creatinine were positively associated with the degree of EPVS in BG.

There were methodological strengths of our study. We recruited participants strictly according to inclusion and exclusion criteria to avoid selection bias. The patients with acute cerebrovascular and cardiovascular disorders were excluded to avoid the impact of the acute stroke, recent myocardial infarction or angina pectoris on blood pressure. The patients with a history of severe ischemic (the largest diameter of infarct size＞20mm on diffusion-weighted imaging and fluid attenuated inversion recovery) or hemorrhagic stroke were excluded because of difficulty and inaccurate assessment on EPVS. In addition, the assessments of EPVS and WMH were performed by two experienced neurologists blinded to clinical information and disagreements were resolved by consensus, which ensure the accuracy of the assessments. We collected

detailed information on vascular confounders, WMH, levels of blood urea nitrogen and creatinine, which are crucial to the interpretation of EPVS[6, 20]. So we think the reliability of the data is high. There were some limitations in our study. First, our study was based on a population who visited the hospital for physical exam in a single center and the cohort may not represent the general population. According to our observation, these people had a higher economic status than that of the general population in China, and some of them showed more symptoms of anxiety. But it's regrettable that we didn't assess the anxiety symptoms by the Hamilton Anxiety Rating Scale or assess the patients' education level. Second, this was a cross-sectional study, and the causal relationship between ABPV and EPVS could not be established. Third, all participants underwent 24-hour ABPM which could only show short-term ABPV. It has been demonstrated that the prognostic significance of BPV on vascular diseases is weaker for short-term than for long-term BPV[21]. Forth, the variables were compared among three categories and the type I error was probably elevated.

This is the first study to investigate the relationship between ABPV and EPVS. Previously, several studies investigated the relationship between EPVS and hypertension. In a prospective, multicenter, hospital-based study, Zhang CQ et al[22] found hypertension was associated with the severity of EPVS in WM, not in BG. Klarenbeek P et al[23] investigated the association between ABP levels and EPVS in first-ever lacunar stroke patients. They found higher day systolic, day diastolic and 24-hour diastolic BP levels were independently associated EPVS in BG, and no relation between ABP levels and EPVS in WM. We also analyzed the correlation between ABP levels and EPVS. We found ABP levels were associated with EPVS in BG, but not in WMH, which is consistent with Klarenbeek P et al.'s study. However, we found only SBP was positively related to higher degree of EPVS in BG in all periods, and no relation between DBP and EPVS, which are different form previous results. The different study population and different scoring methods of assessing EPVS may partly lead to the different results. Our data suggested that SD of SBP, CV of SBP and CV of DBP in all periods were positively associated with the degree of EPVS in BG, but not in WM. The present study couldn't explain the phenomenon.

This may be caused by different pathogenesis of EPVS at the different locations[22, 24, 25]. Previous studies have found the anatomical structure of EPVS located in BG and WM were different[26]. The arteries in the basal ganglia are surrounded by 2 distinct coats of leptomeninges separated by a perivascular space which is continuous with the perivascular space around arteries in the subarachnoid space. Whereas there are only single periarterial layer of leptomeninges surrounding the arteries in the cerebral cortex and they penetrate into the white matter. Drainage of interstitial fluid from the brain to cervical lymph nodes may mainly go along perivascular spaces in WM rather than in BG[3, 27]. In addition, the impact of age, hypertension on EPVS seems to be stronger for EPVS located in BG than for those located in WM[24]. Similarly, the association between EPVS and the load of WMH, taken as a marker of CSVD, also appears to be stronger in BG than in WM. Thus, their dilations may present differences in terms of risk factors as well as in mechanisms in BG and WM. However, the reason SBP is related differently in these two locations remains unclear because there are a very limited number of studies on mechanisms underlying dilation of perivascular spaces in BG and WM. Several studies have demonstrated higher ABPV increased the risk of neuroimaging features of CSVD, such as WMH and lacunar infarction[14, 15]. Our results found higher ABPV was independently associated with higher degree of EPVS in BG, which support the finding that EPVS in BG are a separate marker of CSVD.

An increased permeability of the small vessel walls and blood brain barrier (BBB) are considered to contribute to the development of EPVS, which has been reported to be associated with damage of microvascular endothelial cells and their tight junctions[1, 16, 28]. Higher ABPV would lead to more mechanical stress on the wall vessel, endothelial injury[29] and arterial stiffness[30]. Therefore, it is reasonable that high ABPV contribute to the development of EPVS by damaging endothelial cells. Our results may remind clinicians that they should pay attention to patients' ABPV and lower patients' ABPV in their clinical practices. In the future, a prospective cohort study will help better establish the relationship between ABPV and EPVS.

CONCLUSION

SD of SBP, CV of SBP and CV of DBP during all periods and SD of DBP during nighttime were positively associated with the degree of EPVS in BG. The association was unchanged after adjusting for confounders. No relation was found between ABPV and EPVS in WM. It is important for clinicians to reduce both patients' high blood pressure levels and ABPV.

Contributors WH conceived and designed the experiments. SY, WQ, LY and HF participated in the data collection. JY and YL participated in the analysis of the data. SY drafted the manuscript. WH has given final approval of the version to be published. All authors read and approved the final manuscript.

Funding This work is supported by National Natural Science Foundation of China (Grant No. 81271309).

Conflict of Interest None declared.

Ethic approval The study was approved by the Ethics Committee of Beijing Chaoyang Hospital Affiliated to Capital Medical University and was performed in accordance with the declaration of Helsinki.

Acknowledgements

The authors thank all the study participants.

Data sharing statement We agree to share our data on request. Please contact the corresponding author for access to the data.

Reference

1. Kwee RM, Kwee TC. Virchow-robin spaces at mr imaging. *Radiographics : a review publication of the Radiological Society of North America, Inc*. 2007;27:1071-1086
2. Ozturk MH, Aydingoz U. Comparison of mr signal intensities of cerebral perivascular (virchow-robin) and subarachnoid spaces. *Journal of computer assisted tomography*. 2002;26:902-904
3. Abbott NJ. Evidence for bulk flow of brain interstitial fluid: Significance for physiology and pathology. *Neurochemistry international*. 2004;45:545-552
4. Zhu YC, Dufouil C, Mazoyer B, Soumare A, Ricolfi F, Tzourio C, Chabriat H. Frequency and location of dilated virchow-robin spaces in elderly people: A population-based 3d mr imaging study. *AJNR. American journal of neuroradiology*. 2011;32:709-713
5. Maclullich AM, Wardlaw JM, Ferguson KJ, Starr JM, Seckl JR, Deary IJ. Enlarged perivascular spaces are associated with cognitive function in healthy elderly men. *Journal of neurology, neurosurgery, and psychiatry*. 2004;75:1519-1523
6. Wardlaw JM, Smith EE, Biessels GJ, Cordonnier C, Fazekas F, Frayne R, Lindley RI, O'Brien

JT, Barkhof F, Benavente OR, Black SE, Brayne C, Breteler M, Chabriat H, Decarli C, de Leeuw FE, Doubal F, Duering M, Fox NC, Greenberg S, Hachinski V, Kilimann I, Mok V, Oostenbrugge R, Pantoni L, Speck O, Stephan BC, Teipel S, Viswanathan A, Werring D, Chen C, Smith C, van Buchem M, Norrving B, Gorelick PB, Dichgans M. Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. *The Lancet. Neurology*. 2013;12:822-838

7. Doubal FN, MacLullich AM, Ferguson KJ, Dennis MS, Wardlaw JM. Enlarged perivascular spaces on mri are a feature of cerebral small vessel disease. *Stroke*. 2010;41:450-454

8. Zhu YC, Dufouil C, Soumare A, Mazoyer B, Chabriat H, Tzourio C. High degree of dilated virchow-robin spaces on mri is associated with increased risk of dementia. *Journal of Alzheimer's disease : JAD*. 2010;22:663-672

9. Berezuk C, Ramirez J, Gao F, Scott CJ, Huroy M, Swartz RH, Murray BJ, Black SE, Boulos MI. Virchow-robin spaces: Correlations with polysomnography-derived sleep parameters. *Sleep*. 2015;38:853-858

10. Ohkubo T, Hozawa A, Nagai K, Kikuya M, Tsuji I, Ito S, Satoh H, Hisamichi S, Imai Y. Prediction of stroke by ambulatory blood pressure monitoring versus screening blood pressure measurements in a general population: The ohasama study. *Journal of hypertension*. 2000;18:847-854

11. Shimada K, Kawamoto A, Matsubayashi K, Ozawa T. Silent cerebrovascular disease in the elderly. Correlation with ambulatory pressure. *Hypertension (Dallas, Tex. : 1979)*. 1990;16:692-699

12. Conen D, Bamberg F. Noninvasive 24-h ambulatory blood pressure and cardiovascular disease: A systematic review and meta-analysis. *Journal of hypertension*. 2008;26:1290-1299

13. Rothwell PM. Does blood pressure variability modulate cardiovascular risk? *Current hypertension reports*. 2011;13:177-186

14. Yamaguchi Y, Wada M, Sato H, Nagasawa H, Koyama S, Takahashi Y, Kawanami T, Kato T. Impact of ambulatory blood pressure variability on cerebral small vessel disease progression and cognitive decline in community-based elderly japanese. *American journal of hypertension*. 2014;27:1257-1267

15. Filomena J, Riba-Llena I, Vinyoles E, Tovar JL, Mundet X, Castane X, Vilar A, Lopez-Rueda A, Jimenez-Balado J, Cartanya A, Montaner J, Delgado P. Short-term blood pressure variability relates to the presence of subclinical brain small vessel disease in primary hypertension. *Hypertension (Dallas, Tex. : 1979)*. 2015;66:634-640; discussion 445

16. Wardlaw JM, Smith C, Dichgans M. Mechanisms of sporadic cerebral small vessel disease: Insights from neuroimaging. *The Lancet. Neurology*. 2013;12:483-497

17. Groeschel S, Chong WK, Surtees R, Hanefeld F. Virchow-robin spaces on magnetic resonance images: Normative data, their dilatation, and a review of the literature. *Neuroradiology*. 2006;48:745-754

18. Yao M, Herve D, Jouvent E, Duering M, Reyes S, Godin O, Guichard JP, Dichgans M, Chabriat H. Dilated perivascular spaces in small-vessel disease: A study in cadasil. *Cerebrovascular diseases*. 2014;37:155-163

19. Fazekas F, Chawluk JB, Alavi A, Hurtig HI, Zimmerman RA. Mr signal abnormalities at 1.5 t in alzheimer's dementia and normal aging. *AJR. American journal of roentgenology*. 1987;149:351-356

20. Yamamoto Y, Ohara T, Nagakane Y, Tanaka E, Morii F, Koizumi T, Akiguchi I. Chronic kidney disease, 24-h blood pressure and small vessel diseases are independently associated with cognitive impairment in lacunar infarct patients. *Hypertension research : official journal of the Japanese Society of Hypertension*. 2011;34:1276-1282
21. Rothwell PM, Howard SC, Dolan E, O'Brien E, Dobson JE, Dahlof B, Sever PS, Poulter NR. Prognostic significance of visit-to-visit variability, maximum systolic blood pressure, and episodic hypertension. *Lancet (London, England)*. 2010;375:895-905
22. Zhang C, Chen Q, Wang Y, Zhao X, Wang C, Liu L, Pu Y, Zou X, Du W, Pan Y, Li Z, Jing J, Wang D, Luo Y, Wong KS. Risk factors of dilated virchow-robin spaces are different in various brain regions. *PloS one*. 2014;9:e105505
23. Klarenbeek P, van Oostenbrugge RJ, Lodder J, Rouhl RP, Knottnerus IL, Staals J. Higher ambulatory blood pressure relates to enlarged virchow-robin spaces in first-ever lacunar stroke patients. *Journal of neurology*. 2013;260:115-121
24. Zhu YC, Tzourio C, Soumare A, Mazoyer B, Dufouil C, Chabriat H. Severity of dilated virchow-robin spaces is associated with age, blood pressure, and mri markers of small vessel disease: A population-based study. *Stroke*. 2010;41:2483-2490
25. Satizabal CL, Zhu YC, Dufouil C, Tzourio C. Inflammatory proteins and the severity of dilated virchow-robin spaces in the elderly. *Journal of Alzheimer's disease : JAD*. 2013;33:323-328
26. Pollock H, Hutchings M, Weller RO, Zhang ET. Perivascular spaces in the basal ganglia of the human brain: Their relationship to lacunes. *Journal of anatomy*. 1997;191 (Pt 3):337-346
27. Weller RO, Subash M, Preston SD, Mazanti I, Carare RO. Perivascular drainage of amyloid-beta peptides from the brain and its failure in cerebral amyloid angiopathy and alzheimer's disease. *Brain pathology (Zurich, Switzerland)*. 2008;18:253-266
28. Wuerfel J, Haertle M, Waiczies H, Tysiak E, Bechmann I, Wernecke KD, Zipp F, Paul F. Perivascular spaces--mri marker of inflammatory activity in the brain? *Brain : a journal of neurology*. 2008;131:2332-2340
29. Diaz KM, Veerabhadrappa P, Kashem MA, Thakkar SR, Feairheller DL, Sturgeon KM, Ling C, Williamson ST, Kretzschmar J, Lee H, Grimm H, Babbitt DM, Vin C, Fan X, Crabbe DL, Brown MD. Visit-to-visit and 24-h blood pressure variability: Association with endothelial and smooth muscle function in african americans. *Journal of human hypertension*. 2013;27:671-677
30. Schillaci G, Bilo G, Pucci G, Laurent S, Macquin-Mavier I, Boutouyrie P, Battista F, Settimi L, Desamericq G, Dolbeau G, Faini A, Salvi P, Mannarino E, Parati G. Relationship between short-term blood pressure variability and large-artery stiffness in human hypertension: Findings from 2 large databases. *Hypertension (Dallas, Tex. : 1979)*. 2012;60:369-377

Figure 1. The ABPV metrics of subgroups stratified by EPVS severity in BG during 24-hour. (a) CV of systolic blood pressure. (b) CV of diastolic blood pressure. (c) SD of systolic blood pressure. (d) SD of diastolic blood pressure.

Figure 2. The ABPV metrics of subgroups stratified by EPVS severity in BG during

daytime. (a) CV of systolic blood pressure. (b) CV of diastolic blood pressure. (c) SD of systolic blood pressure. (d) SD of diastolic blood pressure.

Figure 3. The ABPV metrics of subgroups stratified by EPVS severity in BG during nighttime. (a) CV of systolic blood pressure. (b) CV of diastolic blood pressure. (c) SD of systolic blood pressure. (d) SD of diastolic blood pressure.

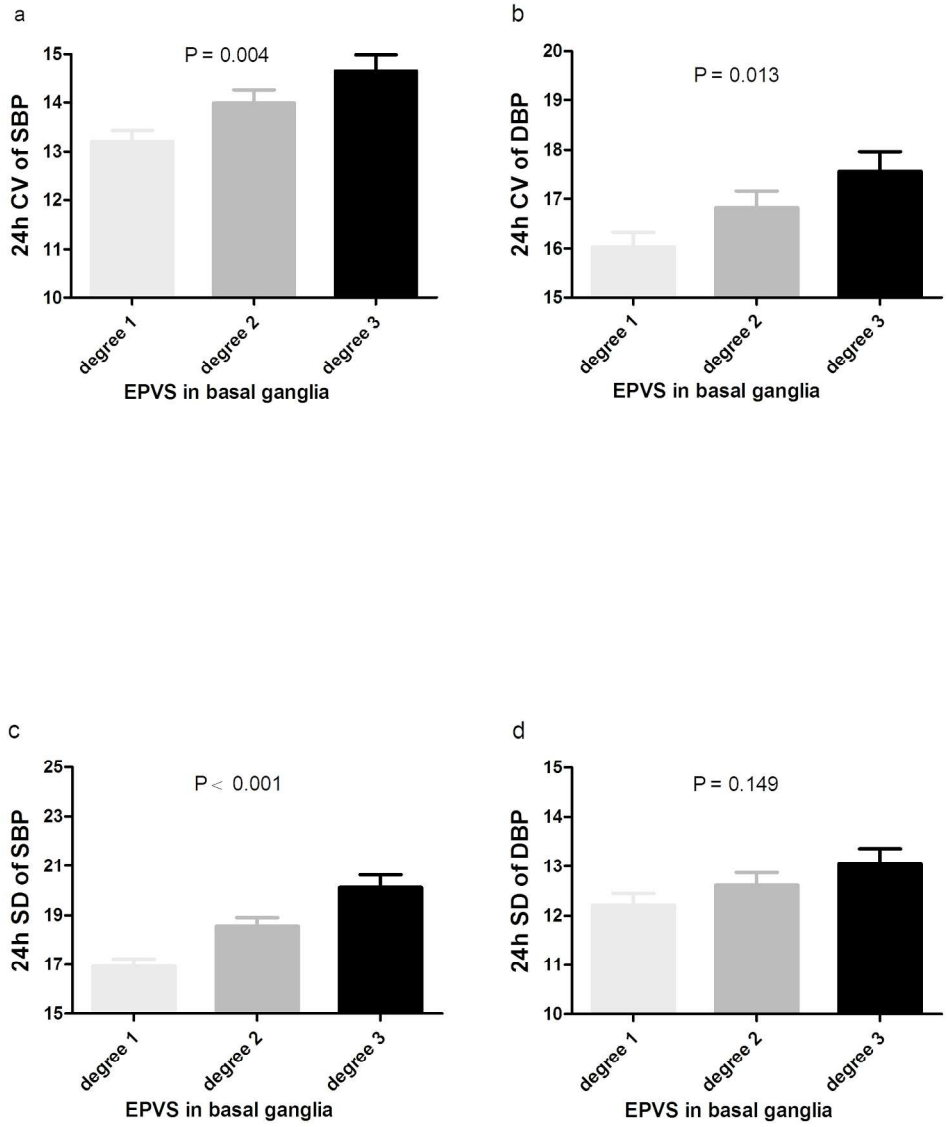


Figure 1. The ABPV metrics of subgroups stratified by EPVS severity in BG during 24-hour. (a) CV of systolic blood pressure. (b) CV of diastolic blood pressure. (c) SD of systolic blood pressure. (d) SD of diastolic blood pressure.

191x228mm (300 x 300 DPI)

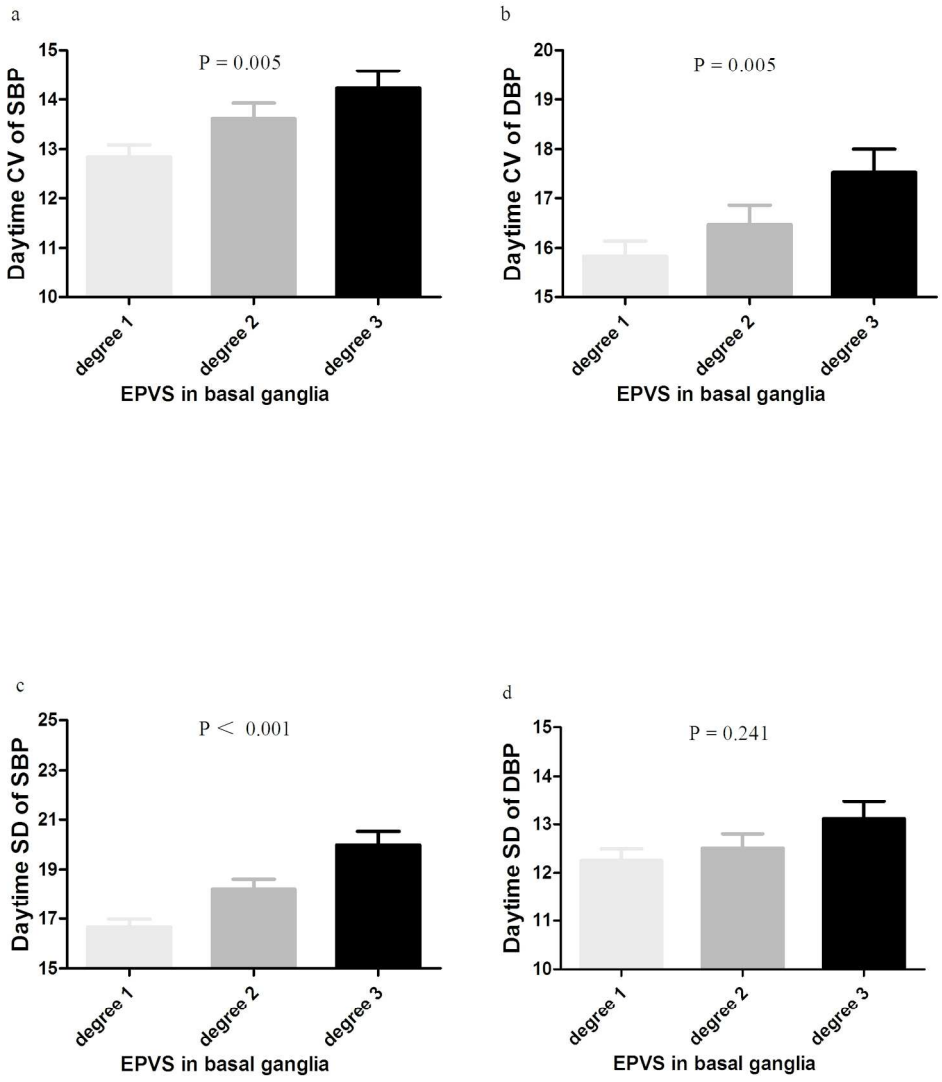


Figure 2. The ABPV metrics of subgroups stratified by EPVS severity in BG during daytime. (a) CV of systolic blood pressure. (b) CV of diastolic blood pressure. (c) SD of systolic blood pressure. (d) SD of diastolic blood pressure.

190x218mm (300 x 300 DPI)

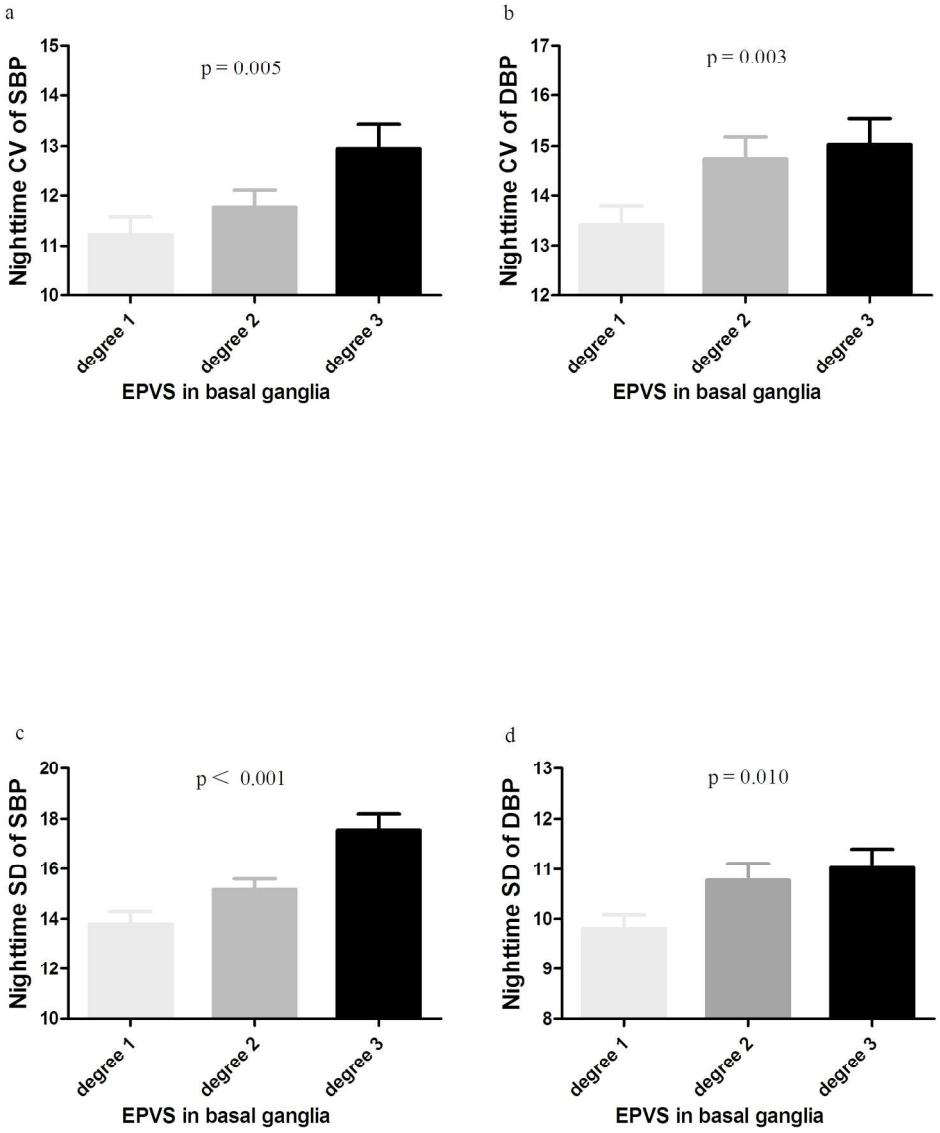


Figure 3. The ABPV metrics of subgroups stratified by EPVS severity in BG during nighttime. (a) CV of systolic blood pressure. (b) CV of diastolic blood pressure. (c) SD of systolic blood pressure. (d) SD of diastolic blood pressure.

189x227mm (300 x 300 DPI)

The comparison of general clinical characteristics between the included and excluded participants

Characteristics	enrolled patients	excluded patients	P
n	573	169	-
Age, years	67.8±14.8	69.6±9.6	0.443
Sex, male (%)	355 (62.0)	101(59.8)	0.607
Current smoking (%)	162 (28.3)	55(32.5)	0.283
Current alcohol (%)	126 (22.0)	42(24.9)	0.435
Hypertension (%)	420 (73.3)	115(68.0)	0.181
Diabetes (%)	191 (33.3)	44(26.0)	0.073
coronary atherosclerosis disease (%)	140 (24.4)	35(20.7)	0.316
body mass index, kg/m^2	25.6±3.5	25.1±3.0	0.160
Using of anti-hypertensive drugs (%)	342 (59.7)	99(58.6)	0.797

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	P1 and 2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	P2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	P3-4
Objectives	3	State specific objectives, including any prespecified hypotheses	P4
Methods			
Study design	4	Present key elements of study design early in the paper	P4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	P4
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	P4
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	P5-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	P5-6
Bias	9	Describe any efforts to address potential sources of bias	P4 and 5

Study size	10	Explain how the study size was arrived at	P4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	P6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	P6
		(*b*) Describe any methods used to examine subgroups and interactions	P6
		(*c*) Explain how missing data were addressed	P6
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	P6
		(b) Give reasons for non-participation at each stage	P6
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	P7
		(b) Indicate number of participants with missing data for each variable of interest	P7
Outcome data	15*	Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	P6-12
		(*b*) Report category boundaries when continuous variables were categorized	

		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	P12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	P12-13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	P13-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	P14-15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	P15

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.